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ZYPREXA[®]
Olanzapine Tablets

ZYPREXA[®] ZYDIS[®]
Olanzapine Orally Disintegrating Tablets

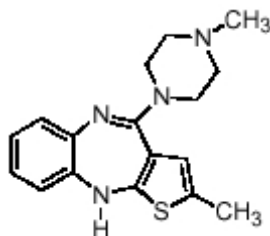
ZYPREXA[®] IntraMuscular
Olanzapine for Injection

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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₄S, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

37 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration
38 only.

39 Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μ mol), 10 mg
40 (32 μ mol), 15 mg (48 μ mol) or 20 mg (64 μ mol). It begins disintegrating in the mouth within
41 seconds, allowing its contents to be subsequently swallowed with or without liquid.

42 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive
43 ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

44 ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

45 Each vial provides for the administration of 10 mg (32 μ mol) olanzapine with inactive
46 ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or
47 sodium hydroxide may have been added during manufacturing to adjust pH.

48 CLINICAL PHARMACOLOGY

49 Pharmacodynamics

50 Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following
51 receptors: serotonin 5HT_{2A/2C}, 5HT₆, (K_i =4, 11, and 5 nM, respectively), dopamine D₁₋₄
52 (K_i =11-31 nM), histamine H₁ (K_i =7 nM), and adrenergic α_1 receptors (K_i =19 nM). Olanzapine is
53 an antagonist with moderate affinity binding for serotonin 5HT₃ (K_i =57 nM) and muscarinic M₁₋₅
54 (K_i =73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA_A, BZD, and β
55 adrenergic receptors (K_i >10 μ M).

56 The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia,
57 is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated
58 through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. The mechanism of
59 action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder
60 is unknown.

61 Antagonism at receptors other than dopamine and 5HT₂ may explain some of the other
62 therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors
63 may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H₁ receptors
64 may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1
65 receptors may explain the orthostatic hypotension observed with this drug.

66 Pharmacokinetics

67 Oral Administration

68 Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours
69 following an oral dose. It is eliminated extensively by first pass metabolism, with approximately
70 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the
71 rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets
72 and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are
73 bioequivalent.

74 Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from
75 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges
76 from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

77 Administration of olanzapine once daily leads to steady-state concentrations in about one week
78 that are approximately twice the concentrations after single doses. Plasma concentrations,
79 half-life, and clearance of olanzapine may vary between individuals on the basis of smoking
80 status, gender, and age (*see* Special Populations).

81 Olanzapine is extensively distributed throughout the body, with a volume of distribution of
82 approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to
83 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

84 Metabolism and Elimination — Following a single oral dose of ^{14}C labeled olanzapine, 7% of
85 the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine
86 is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and
87 feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total
88 radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major
89 circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the
90 concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of
91 the concentration of olanzapine. Both metabolites lack pharmacological activity at the
92 concentrations observed.

93 Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary
94 metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the
95 flavin-containing monooxygenase system are involved in olanzapine oxidation.
96 CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the
97 clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

98 Intramuscular Administration

99 ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations
100 occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a
101 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma
102 concentration approximately 5 times higher than the maximum plasma concentration produced
103 by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is
104 similar to that achieved after oral administration of the same dose. The half-life observed after
105 intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics
106 are linear over the clinical dosing range. Metabolic profiles after intramuscular administration
107 are qualitatively similar to metabolic profiles after oral administration.

108 Special Populations

109 Renal Impairment — Because olanzapine is highly metabolized before excretion and only
110 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact
111 on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were
112 similar in patients with severe renal impairment and normal subjects, indicating that dosage
113 adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is
114 not removed by dialysis. The effect of renal impairment on metabolite elimination has not been
115 studied.

116 Hepatic Impairment — Although the presence of hepatic impairment may be expected to
117 reduce the clearance of olanzapine, a study of the effect of impaired liver function in
118 subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed
119 little effect on the pharmacokinetics of olanzapine.

120 Age — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine
121 was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤ 65 years).
122 Caution should be used in dosing the elderly, especially if there are other factors that might
123 additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND
124 ADMINISTRATION).

125 Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There
126 were, however, no apparent differences between men and women in effectiveness or adverse
127 effects. Dosage modifications based on gender should not be needed.

128 Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers,
129 although dosage modifications are not routinely recommended.

130 Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and
131 Caucasians, especially after normalization for body weight differences. Dosage modifications for
132 race are, therefore, not recommended.

133 Combined Effects — The combined effects of age, smoking, and gender could lead to
134 substantial pharmacokinetic differences in populations. The clearance in young smoking males,
135 for example, may be 3 times higher than that in elderly nonsmoking females. Dosing
136 modification may be necessary in patients who exhibit a combination of factors that may result
137 in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

138 For specific information about the pharmacology of lithium or valproate, refer to the
139 CLINICAL PHARMACOLOGY section of the package inserts for these other products.

140 **CLINICAL EFFICACY DATA**

141 **Schizophrenia**

142 The efficacy of oral olanzapine in the treatment of schizophrenia was established in
143 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for
144 schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the
145 two trials, but this trial did not compare these two drugs on the full range of clinically relevant
146 doses for both.

147 Several instruments were used for assessing psychiatric signs and symptoms in these studies,
148 among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general
149 psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia.
150 The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness,
151 and unusual thought content) is considered a particularly useful subset for assessing actively
152 psychotic schizophrenic patients. A second traditional assessment, the Clinical Global
153 Impression (CGI), reflects the impression of a skilled observer, fully familiar with the
154 manifestations of schizophrenia, about the overall clinical state of the patient. In addition,
155 two more recently developed scales were employed; these included the 30-item Positive and
156 Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the
157 Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the
158 following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative
159 subscale or SANS; and CGI Severity. The results of the trials follow:

160 (1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and
161 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to
162 placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis
163 cluster, on the PANSS Negative subscale, and on CGI Severity.

164 (2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine
165 (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the
166 two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were
167 superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the
168 highest olanzapine dose group was superior to placebo on the SANS. There was no clear
169 advantage for the high dose group over the medium dose group.

170 Examination of population subsets (race and gender) did not reveal any differential
171 responsiveness on the basis of these subgroupings.

172 In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for
173 schizophrenia and who remained stable on olanzapine during open label treatment for at least
174 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to
175 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms
176 of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however,
177 criteria were met for stopping the trial early due to an excess of placebo relapses compared to
178 olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary
179 outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy
180 in patients stabilized for approximately 8 weeks and followed for an observation period of up to
181 8 months.

182 **Bipolar Disorder**

183 Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed
184 episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials
185 in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes.
186 These trials included patients with or without psychotic features and with or without a
187 rapid-cycling course.

188 The primary rating instrument used for assessing manic symptoms in these trials was the
189 Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess
190 the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated
191 mood, speech, increased activity, sexual interest, language/thought disorder, thought content,
192 appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The
193 primary outcome in these trials was change from baseline in the Y-MRS total score. The results
194 of the trials follow:

195 (1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine
196 (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the
197 reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with
198 the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample
199 size and site variability, was not shown to be superior to placebo on this outcome.

200 (2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine
201 (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the
202 reduction of Y-MRS total score.

203 (3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of
204 bipolar disorder who had responded during an initial open-label treatment phase for about two
205 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of
206 olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse.
207 Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and
208 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response
209 during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤ 12
210 and HAM-D 21 to ≤ 8 . Relapse during the double-blind phase was defined as an increase of the
211 Y-MRS or HAM-D 21 total score to ≥ 15 , or being hospitalized for either mania or depression. In
212 the randomized phase, patients receiving continued olanzapine experienced a significantly longer
213 time to relapse.

214 Combination Therapy — The efficacy of oral olanzapine with concomitant lithium or valproate
215 in the treatment of acute manic episodes was established in two controlled trials in patients who

216 met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials
217 included patients with or without psychotic features and with or without a rapid-cycling course.
218 The results of the trials follow:

219 (1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate
220 therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥ 16) were randomized
221 to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine
222 (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or
223 valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 $\mu\text{g/mL}$ to 125 $\mu\text{g/mL}$,
224 respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

225 (2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or
226 valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥ 16) were
227 randomized to receive either olanzapine or placebo, in combination with their original therapy.
228 Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with
229 lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 $\mu\text{g/mL}$ to
230 125 $\mu\text{g/mL}$, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS
231 total score.

232 **Agitation Associated with Schizophrenia and Bipolar I Mania**

233 The efficacy of intramuscular olanzapine for injection for the treatment of agitation was
234 established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated
235 inpatients from two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed
236 episodes). Each of the trials included a single active comparator treatment arm of either
237 haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study).
238 Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically
239 agitated and clinically appropriate candidates for treatment with intramuscular medication, and
240 (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥ 14 on the five items
241 comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor
242 impulse control, tension, hostility, uncooperativeness and excitement items) with at least
243 one individual item score ≥ 4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In
244 the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging
245 from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of
246 agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy
247 measure used for assessing agitation signs and symptoms in these trials was the change from
248 baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to
249 three injections during the 24 hour IM treatment periods; however, patients could not receive the
250 second injection until after the initial 2 hour period when the primary efficacy measure was
251 assessed. The results of the trials follow:

252 (1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for
253 schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg,
254 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS
255 Excited Component at 2 hours post-injection. However, the effect was larger and more consistent
256 for the three highest doses. There were no significant pairwise differences for the 7.5 and 10 mg
257 doses over the 5 mg dose.

258 (2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for
259 schizophrenia (n=311), one fixed intramuscular olanzapine for injection dose of 10 mg was
260 evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited
261 Component at 2 hours post-injection.

262 (3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I
263 Disorder (and currently displaying an acute manic or mixed episode with or without psychotic
264 features) (n=201), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated.
265 Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component
266 at 2 hours post-injection.

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

269 INDICATIONS AND USAGE

270 Schizophrenia

271 Oral ZYPREXA is indicated for the treatment of schizophrenia.

272 The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of
273 schizophrenic inpatients (*see* CLINICAL EFFICACY DATA).

274 The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic
275 patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed
276 for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see*
277 CLINICAL EFFICACY DATA). Nevertheless, the physician who elects to use ZYPREXA for
278 extended periods should periodically re-evaluate the long-term usefulness of the drug for the
279 individual patient (*see* DOSAGE AND ADMINISTRATION).

280 Bipolar Disorder

281 Acute Monotherapy — Oral ZYPREXA is indicated for the treatment of acute mixed or manic
282 episodes associated with Bipolar I Disorder.

283 The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and
284 one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently
285 displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL
286 EFFICACY DATA).

287 Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy
288 with oral ZYPREXA after achieving a responder status for an average duration of two weeks
289 was demonstrated in a controlled trial (*see* CLINICAL EFFICACY DATA). The physician who
290 elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term
291 usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

292 Combination Therapy — The combination of oral ZYPREXA with lithium or valproate is
293 indicated for the short-term treatment of acute mixed or manic episodes associated with Bipolar I
294 Disorder.

295 The efficacy of ZYPREXA in combination with lithium or valproate was established in
296 two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I
297 Disorder who currently displayed an acute manic or mixed episode with or without psychotic
298 features (*see* CLINICAL EFFICACY DATA).

299 Agitation Associated with Schizophrenia and Bipolar I Mania

300 ZYPREXA IntraMuscular is indicated for the treatment of agitation associated with
301 schizophrenia and bipolar I mania. “Psychomotor agitation” is defined in DSM-IV as “excessive
302 motor activity associated with a feeling of inner tension.” Patients experiencing agitation often
303 manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors,
304 escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the
305 use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

306 The efficacy of ZYPREXA IntraMuscular for the treatment of agitation associated with
307 schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled
308 trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes)
309 (*see* CLINICAL EFFICACY DATA).

310 **CONTRAINDICATIONS**

311 ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.
312 For specific information about the contraindications of lithium or valproate, refer to the
313 CONTRAINDICATIONS section of the package inserts for these other products.

314 **WARNINGS**

315 **Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly**
316 **patients with dementia-related psychosis treated with atypical antipsychotic drugs are at**
317 **an increased risk of death compared to placebo. ZYPREXA is not approved for the**
318 **treatment of patients with dementia-related psychosis (*see* BOX WARNING).**

319 In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the
320 incidence of death in olanzapine-treated patients was significantly greater than placebo-treated
321 patients (3.5% vs 1.5%, respectively).

322 **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related**
323 **Psychosis** — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including
324 fatalities, were reported in patients in trials of olanzapine in elderly patients with
325 dementia-related psychosis. In placebo-controlled trials, there was a significantly higher
326 incidence of cerebrovascular adverse events in patients treated with olanzapine compared to
327 patients treated with placebo. Olanzapine is not approved for the treatment of patients with
328 dementia-related psychosis.

329 **Hyperglycemia and Diabetes Mellitus** — Hyperglycemia, in some cases extreme and
330 associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated
331 with atypical antipsychotics including olanzapine. Assessment of the relationship between
332 atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an
333 increased background risk of diabetes mellitus in patients with schizophrenia and the increasing
334 incidence of diabetes mellitus in the general population. Given these confounders, the
335 relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not
336 completely understood. However, epidemiological studies suggest an increased risk of
337 treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical
338 antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated
339 with atypical antipsychotics are not available.

340 Patients with an established diagnosis of diabetes mellitus who are started on atypical
341 antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk
342 factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment
343 with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of
344 treatment and periodically during treatment. Any patient treated with atypical antipsychotics
345 should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia,
346 and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical
347 antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has
348 resolved when the atypical antipsychotic was discontinued; however, some patients required
349 continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

350 **Neuroleptic Malignant Syndrome (NMS)** — A potentially fatal symptom complex sometimes
351 referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with

352 administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are
353 hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability
354 (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional
355 signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and
356 acute renal failure.

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

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

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

371 Tardive Dyskinesia — A syndrome of potentially irreversible, involuntary, dyskinetic
372 movements may develop in patients treated with antipsychotic drugs. Although the prevalence of
373 the syndrome appears to be highest among the elderly, especially elderly women, it is impossible
374 to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
375 patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their
376 potential to cause tardive dyskinesia is unknown.

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

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

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

393 If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug
394 discontinuation should be considered. However, some patients may require treatment with
395 olanzapine despite the presence of the syndrome.

396 For specific information about the warnings of lithium or valproate, refer to the WARNINGS
397 section of the package inserts for these other products.

398

PRECAUTIONS

399 **General**

400 Hemodynamic Effects — Olanzapine may induce orthostatic hypotension associated with
401 dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration
402 period, probably reflecting its α_1 -adrenergic antagonistic properties. Hypotension, bradycardia
403 with or without hypotension, tachycardia, and syncope were also reported during the clinical
404 trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study
405 in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular
406 olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered
407 4 hours apart), approximately one-third of these patients experienced a significant orthostatic
408 decrease in systolic blood pressure (i.e., decrease ≥ 30 mmHg) (*see* DOSAGE AND
409 ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in
410 phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with
411 agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in
412 phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus
413 pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on
414 intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of
415 hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to
416 psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

417 For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized
418 by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual
419 titration to the target dose should be considered if hypotension occurs.

420 For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy
421 or dizzy after injection until examination has indicated that they are not experiencing postural
422 hypotension, bradycardia, and/or hypoventilation.

423 Olanzapine should be used with particular caution in patients with known cardiovascular
424 disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities),
425 cerebrovascular disease, and conditions which would predispose patients to hypotension
426 (dehydration, hypovolemia, and treatment with antihypertensive medications) where the
427 occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased
428 medical risk.

429 Caution is necessary in patients who receive treatment with other drugs having effects that can
430 induce hypotension, bradycardia, respiratory or central nervous system depression (*see* Drug
431 Interactions). Concomitant administration of intramuscular olanzapine and parenteral
432 benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular
433 olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of
434 clinical status for excessive sedation and cardiorespiratory depression is recommended.

435 Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of
436 olanzapine-treated patients. There were confounding factors that may have contributed to the
437 occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients
438 with a history of seizures or with conditions that potentially lower the seizure threshold,
439 e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in
440 a population of 65 years or older.

441 Hyperprolactinemia — As with other drugs that antagonize dopamine D₂ receptors, olanzapine
442 elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue
443 culture experiments indicate that approximately one-third of human breast cancers are prolactin

444 dependent in vitro, a factor of potential importance if the prescription of these drugs is
445 contemplated in a patient with previously detected breast cancer of this type. Although
446 disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported
447 with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels
448 is unknown for most patients. As is common with compounds which increase prolactin release,
449 an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies
450 conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor
451 epidemiologic studies have shown an association between chronic administration of this class of
452 drugs and tumorigenesis in humans; the available evidence is considered too limited to be
453 conclusive.

454 Transaminase Elevations — In placebo-controlled studies, clinically significant ALT (SGPT)
455 elevations (≥ 3 times the upper limit of the normal range) were observed in 2% (6/243) of patients
456 exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients
457 experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite
458 continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In
459 the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for
460 four months after discontinuation, and the other had insufficient follow-up to determine if
461 enzymes normalized.

462 Within the larger premarketing database of about 2400 patients with baseline SGPT ≤ 90 IU/L,
463 the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients
464 experienced jaundice or other symptoms attributable to liver impairment and most had transient
465 changes that tended to normalize while olanzapine treatment was continued.

466 Among 2500 patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued
467 treatment due to transaminase increases.

468 Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or
469 mixed liver injury have also been reported in the postmarketing period.

470 Caution should be exercised in patients with signs and symptoms of hepatic impairment, in
471 patients with pre-existing conditions associated with limited hepatic functional reserve, and in
472 patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of
473 transaminases is recommended in patients with significant hepatic disease (*see* Laboratory
474 Tests).

475 Potential for Cognitive and Motor Impairment — Somnolence was a commonly reported
476 adverse event associated with olanzapine treatment, occurring at an incidence of 26% in
477 olanzapine patients compared to 15% in placebo patients. This adverse event was also dose
478 related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing
479 database.

480 Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should
481 be cautioned about operating hazardous machinery, including automobiles, until they are
482 reasonably certain that olanzapine therapy does not affect them adversely.

483 Body Temperature Regulation — Disruption of the body's ability to reduce core body
484 temperature has been attributed to antipsychotic agents. Appropriate care is advised when
485 prescribing olanzapine for patients who will be experiencing conditions which may contribute to
486 an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat,
487 receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

488 Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic
489 drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with

490 advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used
491 cautiously in patients at risk for aspiration pneumonia.

492 Suicide — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar
493 disorder, and close supervision of high-risk patients should accompany drug therapy.
494 Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with
495 good patient management, in order to reduce the risk of overdose.

496 Use in Patients with Concomitant Illness — Clinical experience with olanzapine in patients
497 with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment
498 *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

499 Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with
500 olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse
501 events possibly related to cholinergic antagonism. Such adverse events were not often the basis
502 for discontinuations from olanzapine, but olanzapine should be used with caution in patients with
503 clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic
504 ileus.

505 In five placebo-controlled studies of olanzapine in elderly patients with dementia-related
506 psychosis (n=1184), the following treatment-emergent adverse events were reported in
507 olanzapine-treated patients at an incidence of at least 2% and significantly greater than
508 placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary
509 incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual
510 hallucinations. The rate of discontinuation due to adverse events was significantly greater with
511 olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated
512 with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not
513 approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to
514 treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX
515 WARNING *and* WARNINGS).

516 Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent
517 history of myocardial infarction or unstable heart disease. Patients with these diagnoses were
518 excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with
519 olanzapine, caution should be observed in cardiac patients (*see* Hemodynamic Effects).

520 For specific information about the precautions of lithium or valproate, refer to the
521 PRECAUTIONS section of the package inserts for these other products.

522 **Information for Patients**

523 Physicians are advised to discuss the following issues with patients for whom they prescribe
524 olanzapine:

525 Orthostatic Hypotension — Patients should be advised of the risk of orthostatic hypotension,
526 especially during the period of initial dose titration and in association with the use of
527 concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or
528 alcohol (*see* Drug Interactions).

529 Interference with Cognitive and Motor Performance — Because olanzapine has the potential to
530 impair judgment, thinking, or motor skills, patients should be cautioned about operating
531 hazardous machinery, including automobiles, until they are reasonably certain that olanzapine
532 therapy does not affect them adversely.

533 Pregnancy — Patients should be advised to notify their physician if they become pregnant or
534 intend to become pregnant during therapy with olanzapine.

535 Nursing — Patients should be advised not to breast-feed an infant if they are taking olanzapine.

536 Concomitant Medication — Patients should be advised to inform their physicians if they are
537 taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for
538 interactions.

539 Alcohol — Patients should be advised to avoid alcohol while taking olanzapine.

540 Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in
541 avoiding overheating and dehydration.

542 Phenylketonurics — ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains
543 phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

544 **Laboratory Tests**

545 Periodic assessment of transaminases is recommended in patients with significant hepatic
546 disease (*see* Transaminase Elevations).

547 **Drug Interactions**

548 The risks of using olanzapine in combination with other drugs have not been extensively
549 evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be
550 used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

551 Because of its potential for inducing hypotension, olanzapine may enhance the effects of
552 certain antihypertensive agents.

553 Olanzapine may antagonize the effects of levodopa and dopamine agonists.

554 The Effect of Other Drugs on Olanzapine — Agents that induce CYP1A2 or glucuronyl
555 transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine
556 clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although
557 olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a
558 single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for
559 induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

560 Charcoal — The administration of activated charcoal (1 g) reduced the C_{max} and AUC of oral
561 olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about
562 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

563 Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and
564 magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

565 Carbamazepine — Carbamazepine therapy (200 mg bid) causes an approximately
566 50% increase in the clearance of olanzapine. This increase is likely due to the fact that
567 carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine
568 may cause an even greater increase in olanzapine clearance.

569 Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine
570 pharmacokinetics.

571 Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean
572 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in
573 olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the
574 overall variability between individuals, and therefore dose modification is not routinely
575 recommended.

576 Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine.
577 This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female
578 nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%,
579 respectively. Lower doses of olanzapine should be considered in patients receiving concomitant
580 treatment with fluvoxamine.

581 Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

582 Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes
583 suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6,
584 and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions
585 mediated by these enzymes.

586 Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of
587 lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of
588 lithium.

589 Valproate — Studies in vitro using human liver microsomes determined that olanzapine has
590 little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further,
591 valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of
592 olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of
593 valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment
594 of valproate.

595 Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active
596 metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics
597 of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the
598 co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic
599 hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the
600 pharmacokinetics of theophylline or its metabolites.

601 Lorazepam — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular
602 olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine,
603 unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular
604 lorazepam and intramuscular olanzapine for injection added to the somnolence observed with
605 either drug alone (*see* Hemodynamic Effects).

606 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

607 Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine
608 was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent
609 to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2,
610 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a
611 mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25,
612 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended
613 human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and
614 hemangiosarcomas was significantly increased in one mouse study in female mice dosed at
615 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m² basis).
616 These tumors were not increased in another mouse study in females dosed at 10 or
617 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m²
618 basis); in this study, there was a high incidence of early mortalities in males of the
619 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was
620 significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at
621 ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m²
622 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels
623 in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity
624 studies; however, measurements during subchronic toxicity studies showed that olanzapine
625 elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity
626 study. An increase in mammary gland neoplasms has been found in rodents after chronic
627 administration of other antipsychotic drugs and is considered to be prolactin mediated. The

628 relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is
629 unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

630 **Mutagenesis** — No evidence of mutagenic potential for olanzapine was found in the Ames
631 reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in
632 Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of
633 forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in
634 bone marrow of Chinese hamsters.

635 **Impairment of Fertility** — In an oral fertility and reproductive performance study in rats, male
636 mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female
637 fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended
638 human daily oral dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment
639 reversed the effects on male mating performance. In female rats, the precoital period was
640 increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended
641 human daily oral dose on a mg/m² basis). Diestrus was prolonged and estrus delayed at
642 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis);
643 therefore olanzapine may produce a delay in ovulation.

644 **Pregnancy**

645 **Pregnancy Category C** — In oral reproduction studies in rats at doses up to 18 mg/kg/day and
646 in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily
647 oral dose on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In an oral
648 rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed
649 at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a
650 mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended
651 human daily oral dose on a mg/m² basis). In an oral rabbit teratology study, fetal toxicity
652 (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic
653 dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m²
654 basis).

655 Placental transfer of olanzapine occurs in rat pups.

656 There are no adequate and well-controlled trials with olanzapine in pregnant females.
657 Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in
658 normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic
659 abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always
660 predictive of human response, this drug should be used during pregnancy only if the potential
661 benefit justifies the potential risk to the fetus.

662 **Labor and Delivery**

663 Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and
664 delivery in humans is unknown.

665 **Nursing Mothers**

666 In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant
667 dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is
668 recommended that women receiving olanzapine should not breast-feed.

669 **Pediatric Use**

670 Safety and effectiveness in pediatric patients have not been established.

671 **Geriatric Use**

672 Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were
673 65 years of age or over. In patients with schizophrenia, there was no indication of any different
674 tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients
675 with dementia-related psychosis have suggested that there may be a different tolerability profile
676 in this population compared to younger patients with schizophrenia. Elderly patients with
677 dementia-related psychosis treated with olanzapine are at an increased risk of death compared to
678 placebo. Olanzapine is not approved for the treatment of patients with dementia-related
679 psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis,
680 vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic
681 clearance or increase the pharmacodynamic response to olanzapine should lead to consideration
682 of a lower starting dose for any geriatric patient (*see* BOX WARNING, WARNINGS,
683 PRECAUTIONS, *and* DOSAGE AND ADMINISTRATION).

684 **ADVERSE REACTIONS**

685 The information below is derived from a clinical trial database for olanzapine consisting of
686 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and
687 722 patients with exposure to intramuscular olanzapine for injection. This database includes:
688 (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in
689 schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of
690 exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine
691 premarketing bipolar mania trials representing approximately 66 patient-years of exposure;
692 (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric
693 symptoms in association with Alzheimer's disease representing approximately 29 patient-years
694 of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of
695 December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for
696 injection premarketing trials in agitated patients with schizophrenia, Bipolar I Disorder (manic or
697 mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical
698 study database for olanzapine in combination with lithium or valproate, consisting of
699 224 patients who participated in bipolar mania trials with approximately 22 patient-years of
700 exposure, is included below.

701 The conditions and duration of treatment with olanzapine varied greatly and included (in
702 overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients,
703 fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions
704 were assessed by collecting adverse events, results of physical examinations, vital signs, weights,
705 laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

706 Certain portions of the discussion below relating to objective or numeric safety parameters,
707 namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and
708 ECG changes are derived from studies in patients with schizophrenia and have not been
709 duplicated for bipolar mania or agitation. However, this information is also generally applicable
710 to bipolar mania and agitation.

711 Adverse events during exposure were obtained by spontaneous report and recorded by clinical
712 investigators using terminology of their own choosing. Consequently, it is not possible to
713 provide a meaningful estimate of the proportion of individuals experiencing adverse events
714 without first grouping similar types of events into a smaller number of standardized event
715 categories. In the tables and tabulations that follow, standard COSTART dictionary terminology
716 has been used initially to classify reported adverse events.

717 The stated frequencies of adverse events represent the proportion of individuals who
718 experienced, at least once, a treatment-emergent adverse event of the type listed. An event was
719 considered treatment emergent if it occurred for the first time or worsened while receiving
720 therapy following baseline evaluation. The reported events do not include those event terms that
721 were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated
722 below. It is important to emphasize that, although the events occurred during treatment with
723 olanzapine, they were not necessarily caused by it. The entire label should be read to gain a
724 complete understanding of the safety profile of olanzapine.

725 The prescriber should be aware that the figures in the tables and tabulations cannot be used to
726 predict the incidence of side effects in the course of usual medical practice where patient
727 characteristics and other factors differ from those that prevailed in the clinical trials. Similarly,
728 the cited frequencies cannot be compared with figures obtained from other clinical investigations
729 involving different treatments, uses, and investigators. The cited figures, however, do provide the
730 prescribing physician with some basis for estimating the relative contribution of drug and
731 nondrug factors to the adverse event incidence in the population studied.

732 **Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination** 733 **Trials**

734 The following findings are based on premarketing trials of (1) oral olanzapine for
735 schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric symptoms
736 in association with Alzheimer's disease, and premarketing combination trials, and
737 (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar
738 mania.

739 **Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-** 740 **Controlled Trials**

741 Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to
742 adverse events (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to
743 increases in SGPT were considered to be drug related (2% for oral olanzapine vs 0% for placebo)
744 (*see* PRECAUTIONS).

745 Bipolar Mania Monotherapy — Overall, there was no difference in the incidence of
746 discontinuation due to adverse events (2% for oral olanzapine vs 2% for placebo).

747 Agitation — Overall, there was no difference in the incidence of discontinuation due to
748 adverse events (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

749 **Adverse Events Associated with Discontinuation of Treatment in Short-Term** 750 **Combination Trials**

751 Bipolar Mania Combination Therapy — In a study of patients who were already tolerating
752 either lithium or valproate as monotherapy, discontinuation rates due to adverse events were
753 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for
754 patients who remained on lithium or valproate monotherapy. Discontinuations with the
755 combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient
756 were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

757 **Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials**

758 The most commonly observed adverse events associated with the use of oral olanzapine
759 (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated
760 patients (olanzapine incidence at least twice that for placebo) were:
761

762 **Common Treatment-Emergent Adverse Events Associated with the**
763 **Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder ¹	8	4
Akathisia	5	1

764 ¹ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
765

766 **Common Treatment-Emergent Adverse Events Associated with the**
767 **Use of Oral Olanzapine in 3-Week and 4-Week Trials — BIPOLAR MANIA**

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

768
769 There was one adverse event (somnolence) observed at an incidence of 5% or greater among
770 intramuscular olanzapine for injection-treated patients and not observed at an equivalent
771 incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo)
772 during the placebo-controlled premarketing studies. The incidence of somnolence during the
773 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar
774 mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

775 **Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-**
776 **Treated Patients in Short-Term, Placebo-Controlled Trials**

777 Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
778 adverse events that occurred in 2% or more of patients treated with oral olanzapine (doses
779 ≥ 2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of
780 placebo-controlled trials.

781

782

783

784

785

Table 1
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials¹
with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=532)	Placebo (N=294)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9

Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

786 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
787 incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression,
788 diarrhea, dysmenorrhea (denominator used was for females only [olanzapine, N=201; placebo, N=114]),
789 hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality
790 disorder (COSTART term for designating non-aggressive objectionable behavior), rash, thinking abnormal, weight
791 loss.
792

793 Commonly Observed Adverse Events in Short-Term Combination Trials

794 In the bipolar mania combination placebo-controlled trials, the most commonly observed
795 adverse events associated with the combination of olanzapine and lithium or valproate (incidence
796 of $\geq 5\%$ and at least twice placebo) were:
797

798 Common Treatment-Emergent Adverse Events Associated with the 799 Use of Oral Olanzapine in 6-Week Combination Trials — BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Dry mouth	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

800

801 Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-
802 Treated Patients in Short-Term Combination Trials

803 Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
804 adverse events that occurred in 2% or more of patients treated with the combination of
805 olanzapine (doses ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or
806 valproate alone who participated in the acute phase of placebo-controlled combination trials.
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Table 2
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials¹
with Oral Olanzapine

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7

Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea ²	2	0
Vaginitis ²	2	0

812 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
813 incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation,
814 akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence,
815 flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder (denominator
816 used was for females only [olanzapine, N=128; placebo, N=51]), myalgia, nausea, nervousness, pain, paranoid
817 reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.

818 ² Denominator used was for females only (olanzapine, N=128; placebo, N=51).

819

820 For specific information about the adverse reactions observed with lithium or valproate, refer
821 to the ADVERSE REACTIONS section of the package inserts for these other products.

822 **Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular**
823 **Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials**

824 Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
825 adverse events that occurred in 1% or more of patients treated with intramuscular olanzapine for
826 injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who
827 participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or
828 bipolar mania.

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Table 3
Treatment-Emergent Adverse Events:
Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials
with Intramuscular Olanzapine for Injection
in Agitated Patients with Schizophrenia or Bipolar Mania¹

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=415)	Placebo (N=150)
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		

Somnolence	6	3
Dizziness	4	2
Tremor	1	0

835 ¹ Events reported by at least 1% of patients treated with olanzapine for injection, except the following events which
836 had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia,
837 nervousness.
838

839 **Additional Findings Observed in Clinical Trials**

840 The following findings are based on clinical trials.

841 **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials**

842 Extrapyramidal Symptoms — The following table enumerates the percentage of patients with
843 treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal
844 rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at
845 3 fixed doses with placebo in the treatment of schizophrenia.

846
847 **Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence**
848 **in a Fixed Dosage Range, Placebo-Controlled Clinical Trial**
849 **of Oral Olanzapine in Schizophrenia — Acute Phase***

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism ¹	15	14	12	14
Akathisia ²	23	16	19	27

850 * No statistically significant differences.
851 ¹ Percentage of patients with a Simpson-Angus Scale total score >3.
852 ² Percentage of patients with a Barnes Akathisia Scale global score ≥2.
853

854 The following table enumerates the percentage of patients with treatment-emergent
855 extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute
856 therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo
857 in the treatment of schizophrenia.
858

859 **Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence**
860 **in a Fixed Dosage Range, Placebo-Controlled Clinical Trial**
861 **of Oral Olanzapine in Schizophrenia — Acute Phase**

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events ¹	1	3	2	3
Parkinsonism events ²	10	8	14	20
Akathisia events ³	1	5	11*	10*
Dyskinetic events ⁴	4	0	2	1
Residual events ⁵	1	2	5	1
Any extrapyramidal event	16	15	25	32*

- 862 * Statistically significantly different from placebo.
 863 ¹ Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck
 864 rigidity, oculogyric crisis, opisthotonos, torticollis.
 865 ² Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity,
 866 extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
 867 ³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
 868 ⁴ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome,
 869 choreoathetosis, dyskinesia, tardive dyskinesia.
 870 ⁵ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus,
 871 twitching.

872
 873 The following table enumerates the percentage of patients with treatment-emergent
 874 extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during
 875 controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with
 876 placebo in agitation. Patients in each dose group could receive up to three injections during the
 877 trials (*see* CLINICAL EFFICACY DATA). Patient assessments were conducted during the
 878 24 hours following the initial dose of intramuscular olanzapine for injection. There were no
 879 statistically significant differences from placebo.

880
 881 **Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence**
 882 **in a Fixed Dose, Placebo-Controlled Clinical Trial**
 883 **of Intramuscular Olanzapine for Injection**
 884 **in Agitated Patients with Schizophrenia***

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism ¹	0	0	0	0	3
Akathisia ²	0	0	5	0	0

- 885 * No statistically significant differences.
 886 ¹ Percentage of patients with a Simpson-Angus total score >3.
 887 ² Percentage of patients with a Barnes Akathisia Scale global score ≥2.

888
 889 The following table enumerates the percentage of patients with treatment-emergent
 890 extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same
 891 controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with
 892 placebo in agitated patients with schizophrenia. There were no statistically significant differences
 893 from placebo.

894
 895 **Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence**
 896 **in a Fixed Dose, Placebo-Controlled Clinical Trial**
 897 **of Intramuscular Olanzapine for Injection**
 898 **in Agitated Patients with Schizophrenia***

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events ¹	0	0	0	0	0
Parkinsonism events ²	0	4	2	0	0
Akathisia events ³	0	2	0	0	0

Dyskinetic events ⁴	0	0	0	0	0
Residual events ⁵	0	0	0	0	0
Any extrapyramidal event	0	4	2	0	0

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- * No statistically significant differences.
¹ Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
² Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
⁴ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
⁵ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events — The following table addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

Adverse Event	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

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Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain — In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

936 Given the concern about neutropenia associated with other psychotropic compounds and the
937 finding of leukopenia associated with the administration of olanzapine in several animal models
938 (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic
939 parameters in premarketing studies with olanzapine. There was no indication of a risk of
940 clinically significant neutropenia associated with olanzapine treatment in the premarketing
941 database for this drug.

942 In clinical trials among olanzapine-treated patients with random triglyceride levels of
943 <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of
944 ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185)
945 had a mean increase of 20 mg/dL in triglycerides from a mean baseline value of 175 mg/dL.

946 In placebo-controlled trials, olanzapine-treated patients with random cholesterol levels of
947 <200 mg/dL at baseline (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during
948 the trials more often than placebo-treated patients (N=602) (3.6% vs 2.2%, respectively). In these
949 same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in
950 cholesterol from a mean baseline value of 203 mg/dL, which was significantly different
951 compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean
952 baseline value of 203 mg/dL.

953 *ECG Changes* — Between-group comparisons for pooled placebo-controlled trials revealed no
954 statistically significant olanzapine/placebo differences in the proportions of patients experiencing
955 potentially important changes in ECG parameters, including QT, QTc, and PR intervals.
956 Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute
957 compared to no change among placebo patients. This slight tendency to tachycardia may be
958 related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

959 **Other Adverse Events Observed During the Clinical Trial Evaluation of** 960 **Olanzapine**

961 Following is a list of terms that reflect treatment-emergent adverse events reported by patients
962 treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8661 patients,
963 4165 patient-years of exposure). This listing may not include those events already listed in
964 previous tables or elsewhere in labeling, those events for which a drug cause was remote, those
965 event terms which were so general as to be uninformative, and those events reported only once
966 or twice which did not have a substantial probability of being acutely life-threatening.

967 Events are further categorized by body system and listed in order of decreasing frequency
968 according to the following definitions: frequent adverse events are those occurring in at least
969 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
970 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients;
971 rare events are those occurring in fewer than 1/1000 patients.

972 **Body as a Whole** — *Frequent*: dental pain and flu syndrome; *Infrequent*: abdomen enlarged,
973 chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain,
974 photosensitivity reaction, and suicide attempt; *Rare*: chills and fever, hangover effect, and
975 sudden death.

976 **Cardiovascular System** — *Frequent*: hypotension; *Infrequent*: atrial fibrillation, bradycardia,
977 cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor,
978 palpitation, vasodilatation, and ventricular extrasystoles; *Rare*: arteritis, heart failure, and
979 pulmonary embolus.

980 **Digestive System** — *Frequent*: flatulence, increased salivation, and thirst;
981 *Infrequent*: dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis,

982 gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal
983 abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare*: aphthous
984 stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty
985 deposit, and tongue discoloration.

986 **Endocrine System** — *Infrequent*: diabetes mellitus; *Rare*: diabetic acidosis and goiter.

987 **Hemic and Lymphatic System** — *Infrequent*: anemia, cyanosis, leukocytosis, leukopenia,
988 lymphadenopathy, and thrombocytopenia; *Rare*: normocytic anemia and thrombocythemia.

989 **Metabolic and Nutritional Disorders** — *Infrequent*: acidosis, alkaline phosphatase increased,
990 bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia,
991 hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema;
992 *Rare*: gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication.

993 **Musculoskeletal System** — *Frequent*: joint stiffness and twitching; *Infrequent*: arthritis,
994 arthrosis, leg cramps, and myasthenia; *Rare*: bone pain, bursitis, myopathy, osteoporosis, and
995 rheumatoid arthritis.

996 **Nervous System** — *Frequent*: abnormal dreams, amnesia, delusions, emotional lability,
997 euphoria, manic reaction, paresthesia, and schizophrenic reaction; *Infrequent*: akinesia, alcohol
998 misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia,
999 depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia,
1000 incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias,
1001 somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal
1002 syndrome; *Rare*: circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy,
1003 nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

1004 **Respiratory System** — *Frequent*: dyspnea; *Infrequent*: apnea, asthma, epistaxis, hemoptysis,
1005 hyperventilation, hypoxia, laryngitis, and voice alteration; *Rare*: atelectasis, hiccup,
1006 hypoventilation, lung edema, and stridor.

1007 **Skin and Appendages** — *Frequent*: sweating; *Infrequent*: alopecia, contact dermatitis, dry
1008 skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria,
1009 and vesiculobullous rash; *Rare*: hirsutism and pustular rash.

1010 **Special Senses** — *Frequent*: conjunctivitis; *Infrequent*: abnormality of accommodation,
1011 blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation,
1012 eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare*: corneal lesion,
1013 glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment
1014 deposits lens.

1015 **Urogenital System** — *Frequent*: vaginitis^{*}; *Infrequent*: abnormal ejaculation^{*}, amenorrhea^{*},
1016 breast pain, cystitis, decreased menstruation^{*}, dysuria, female lactation^{*}, glycosuria,
1017 gynecomastia, hematuria, impotence^{*}, increased menstruation^{*}, menorrhagia^{*}, metrorrhagia^{*},
1018 polyuria, premenstrual syndrome^{*}, pyuria, urinary frequency, urinary retention, urinary urgency,
1019 urination impaired, uterine fibroids enlarged^{*}, and vaginal hemorrhage^{*}; *Rare*: albuminuria,
1020 breast enlargement, mastitis, and oliguria.

1021 ^{*} Adjusted for gender.

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1023 Following is a list of terms that reflect treatment-emergent adverse events reported by patients
1024 treated with intramuscular olanzapine for injection (at one or more doses ≥ 2.5 mg/injection) in
1025 clinical trials (722 patients). This listing may not include those events already listed in previous
1026 tables or elsewhere in labeling, those events for which a drug cause was remote, those event
1027 terms which were so general as to be uninformative, and those events reported only once which
1028 did not have a substantial probability of being acutely life-threatening.

1029 Events are further categorized by body system and listed in order of decreasing frequency
1030 according to the following definitions: frequent adverse events are those occurring in at least
1031 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
1032 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

1033 **Body as a Whole** — *Frequent*: injection site pain; *Infrequent*: abdominal pain and fever.

1034 **Cardiovascular System** — *Infrequent*: AV block, heart block, and syncope.

1035 **Digestive System** — *Infrequent*: diarrhea and nausea.

1036 **Hemic and Lymphatic System** — *Infrequent*: anemia.

1037 **Metabolic and Nutritional Disorders** — *Infrequent*: creatine phosphokinase increased,
1038 dehydration, and hyperkalemia.

1039 **Musculoskeletal System** — *Infrequent*: twitching.

1040 **Nervous System** — *Infrequent*: abnormal gait, akathisia, articulation impairment, confusion,
1041 and emotional lability.

1042 **Skin and Appendages** — *Infrequent*: sweating.

1043 **Postintroduction Reports**

1044 Adverse events reported since market introduction that were temporally (but not necessarily
1045 causally) related to ZYPREXA therapy include the following: allergic reaction
1046 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice,
1047 pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including
1048 pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥ 240 mg/dL
1049 and random triglyceride levels of ≥ 1000 mg/dL have been rarely reported.

1050 **DRUG ABUSE AND DEPENDENCE**

1051 **Controlled Substance Class**

1052 Olanzapine is not a controlled substance.

1053 **Physical and Psychological Dependence**

1054 In studies prospectively designed to assess abuse and dependence potential, olanzapine was
1055 shown to have acute depressive CNS effects but little or no potential of abuse or physical
1056 dependence in rats administered oral doses up to 15 times the maximum recommended human
1057 daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum
1058 recommended human daily oral dose on a mg/m^2 basis.

1059 Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance,
1060 or physical dependence. While the clinical trials did not reveal any tendency for any
1061 drug-seeking behavior, these observations were not systematic, and it is not possible to predict
1062 on the basis of this limited experience the extent to which a CNS-active drug will be misused,
1063 diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for
1064 a history of drug abuse, and such patients should be observed closely for signs of misuse or
1065 abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

1066 **OVERDOSAGE**

1067 **Human Experience**

1068 In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or
1069 intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the
1070 largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred
1071 speech. In the limited number of patients who were evaluated in hospitals, including the patient

1072 taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or
1073 ECG. Vital signs were usually within normal limits following overdoses.

1074 In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in
1075 the majority of cases. In symptomatic patients, symptoms with $\geq 10\%$ incidence included
1076 agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced
1077 level of consciousness ranging from sedation to coma. Among less commonly reported
1078 symptoms were the following potentially medically serious events: aspiration, cardiopulmonary
1079 arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing
1080 sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic
1081 malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension.
1082 Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine
1083 alone. In one case of death, the amount of acutely ingested olanzapine was reported to be
1084 possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute
1085 olanzapine ingestion of 1500 mg.

1086 **Overdosage Management**

1087 The possibility of multiple drug involvement should be considered. In case of acute
1088 overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation,
1089 which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and
1090 administration of activated charcoal together with a laxative should be considered. The
1091 possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose
1092 may create a risk of aspiration with induced emesis. Cardiovascular monitoring should
1093 commence immediately and should include continuous electrocardiographic monitoring to detect
1094 possible arrhythmias.

1095 There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should
1096 be initiated. Hypotension and circulatory collapse should be treated with appropriate measures
1097 such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine,
1098 or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen
1099 hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and
1100 monitoring should continue until the patient recovers.

1101 **DOSAGE AND ADMINISTRATION**

1102 **Schizophrenia**

1103 Usual Dose — Oral olanzapine should be administered on a once-a-day schedule without
1104 regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day
1105 within several days. Further dosage adjustments, if indicated, should generally occur at intervals
1106 of not less than 1 week, since steady state for olanzapine would not be achieved for
1107 approximately 1 week in the typical patient. When dosage adjustments are necessary, dose
1108 increments/decrements of 5 mg QD are recommended.

1109 Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical
1110 trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the
1111 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of
1112 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above
1113 20 mg/day has not been evaluated in clinical trials.

1114 Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are
1115 debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a
1116 combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking

1117 female patients ≥ 65 years of age), or who may be more pharmacodynamically sensitive to
1118 olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant
1119 Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should
1120 be performed with caution in these patients.

1121 Maintenance Treatment — While there is no body of evidence available to answer the question
1122 of how long the patient treated with olanzapine should remain on it, the effectiveness of oral
1123 olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients
1124 who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a
1125 period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL
1126 EFFICACY DATA). Patients should be periodically reassessed to determine the need for
1127 maintenance treatment with appropriate dose.

1128 **Bipolar Disorder**

1129 Usual Monotherapy Dose — Oral olanzapine should be administered on a once-a-day schedule
1130 without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated,
1131 should generally occur at intervals of not less than 24 hours, reflecting the procedures in the
1132 placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements
1133 of 5 mg QD are recommended.

1134 Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
1135 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
1136 clinical trials.

1137 Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy
1138 with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an
1139 average duration of two weeks, was demonstrated in a controlled trial (*see* CLINICAL
1140 EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should
1141 periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1142 Bipolar Mania Usual Dose in Combination with Lithium or Valproate — When administered
1143 in combination with lithium or valproate, oral olanzapine dosing should generally begin with
1144 10 mg once-a-day without regard to meals.

1145 Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
1146 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
1147 clinical trials.

1148 Dosing in Special Populations — *See* Dosing in Special Populations *under* DOSAGE AND
1149 ADMINISTRATION, Schizophrenia.

1150 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

1151 After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately
1152 upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in
1153 the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or
1154 without liquid.

1155 **Agitation Associated with Schizophrenia and Bipolar I Mania**

1156 Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania — The efficacy of
1157 intramuscular olanzapine for injection in controlling agitation in these disorders was
1158 demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is
1159 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (*see*
1160 CLINICAL EFFICACY DATA). If agitation warranting additional intramuscular doses persists
1161 following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of

1162 repeated doses of intramuscular olanzapine for injection in agitated patients has not been
1163 systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater
1164 than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and
1165 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of
1166 intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be
1167 associated with a substantial occurrence of significant orthostatic hypotension (*see*
1168 PRECAUTIONS, Hemodynamic Effects). Thus, it is recommended that patients requiring
1169 subsequent intramuscular injections be assessed for orthostatic hypotension prior to the
1170 administration of any subsequent doses of intramuscular olanzapine for injection. The
1171 administration of an additional dose to a patient with a clinically significant postural change in
1172 systolic blood pressure is not recommended.

1173 If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a
1174 range of 5-20 mg/day as soon as clinically appropriate (*see* Schizophrenia or Bipolar Disorder
1175 *under* DOSAGE AND ADMINISTRATION).

1176 Intramuscular Dosing in Special Populations — A dose of 5 mg per injection should be
1177 considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg
1178 per injection should be considered for patients who otherwise might be debilitated, be
1179 predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine
1180 (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and
1181 Drug Interactions *under* PRECAUTIONS).

1182 Administration of ZYPREXA IntraMuscular

1183 ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer
1184 intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

1185 Parenteral drug products should be inspected visually for particulate matter and discoloration
1186 prior to administration, whenever solution and container permit.

1187 Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection

1188 Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a
1189 solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear
1190 clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should
1191 be used immediately (within 1 hour) after reconstitution. **Discard any unused portion.**

1192 The following table provides injection volumes for delivering various doses of intramuscular
1193 olanzapine for injection reconstituted with Sterile Water for Injection.

1194

<u>Dose, mg Olanzapine</u>	<u>Volume of Injection, mL</u>
10	Withdraw total contents of vial
7.5	1.5
5	1
2.5	0.5

1195

1196 Physical Incompatibility Information

1197 ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection.

1198 ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because
1199 precipitation occurs when these products are mixed. Lorazepam injection should not be used to
1200 reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution

1201 time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection
1202 because the resulting low pH has been shown to degrade olanzapine over time.

1203 **HOW SUPPLIED**

1204 The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in
1205 blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with
1206 LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and
1207 tablet number. The tablets are available as follows:
1208

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 30	NDC 0002- 4112-30	NDC 0002- 4115-30	NDC 0002- 4116-30	NDC 0002- 4117-30	NDC 0002- 4415-30	NDC 0002- 4420-30
Bottles 60	NDC 0002- 4112-60	NDC 0002- 4115-60	NDC 0002- 4116-60	NDC 0002- 4117-60	NDC 0002- 4415-60	NDC 0002- 4420-60
Blisters - ID* 100	NDC 0002- 4112-33	NDC 0002- 4115-33	NDC 0002- 4116-33	NDC 0002- 4117-33	NDC 0002- 4415-33	NDC 0002- 4420-33
Bottles 1000	NDC 0002- 4112-04	NDC 0002- 4115-04	NDC 0002- 4116-04	NDC 0002- 4117-04	NDC 0002- 4415-04	NDC 0002- 4420-04

1209 * Identi-Dose® (unit dose medication, Lilly).
1210

1211 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed
1212 with the tablet strength. The tablets are available as follows:
1213

ZYPREXA ZYDIS Tablets*	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 30 (Child-Resistant)	NDC 0002- 4453-85	NDC 0002- 4454-85	NDC 0002- 4455-85	NDC 0002- 4456-85

1214
1215 ZYPREXA is a registered trademark of Eli Lilly and Company.

1216 ZYDIS is a registered trademark of Cardinal Health, Inc. or one of its subsidiaries.

1217 *ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and
1218 Company by Cardinal Health, United Kingdom, SN5 8RU.
1219

1220 ZYPREXA IntraMuscular is available in:

1221 NDC 0002-7597-01 (No. VL7597) - 10 mg vial (1s)
1222

1223 Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before
1224 reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

1225 Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature,
1226 20° to 25°C (68° to 77°F) [see USP] for up to 1 hour if necessary. **Discard any unused portion**
1227 **of reconstituted ZYPREXA IntraMuscular.** The USP defines controlled room temperature as
1228 a temperature maintained thermostatically that encompasses the usual and customary working

1229 environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated
1230 to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F)
1231 that are experienced in pharmacies, hospitals, and warehouses.

1232 Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect
1233 ZYPREXA IntraMuscular from light, do not freeze.

1234 **ANIMAL TOXICOLOGY**

1235 In animal studies with olanzapine, the principal hematologic findings were reversible
1236 peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum
1237 recommended human daily oral dose on a mg/m² basis), dose-related decreases in lymphocytes
1238 and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed
1239 reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of
1240 treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses
1241 of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m²
1242 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased
1243 body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended
1244 human daily oral dose on a mg/m² basis) for 3 months or 16 mg/kg (8 times the maximum
1245 recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone
1246 marrow cytotoxicity was found in any of the species examined. Bone marrows were
1247 normocellular or hypercellular, indicating that the reductions in circulating blood cells were
1248 probably due to peripheral (non-marrow) factors.

1249 Literature revised March 20, 2006

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1252 **www.ZYPREXA.com**

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