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ZYPREXA[®]
Olanzapine Tablets

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

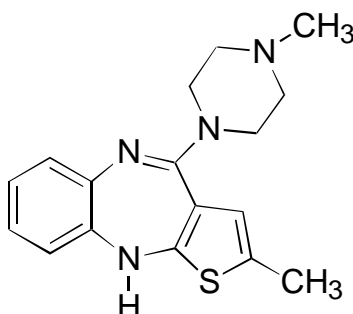
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ZYPREXA[®] IntraMuscular
Olanzapine for Injection

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DESCRIPTION

11 ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine
12 class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*]
13 [1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₄S, which corresponds to a molecular
14 weight of 312.44. The chemical structure is:



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

16 ZYPREXA tablets are intended for oral administration only.

17 Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg
18 (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are
19 carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium
20 stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains
21 Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red
22 Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which
23 contains FD&C Blue No. 2 Aluminum Lake.

24 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration
25 only.

26 Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg
27 (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within
28 seconds, allowing its contents to be subsequently swallowed with or without liquid.

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

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

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

CLINICAL PHARMACOLOGY

35

36 Pharmacodynamics

37 Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following
38 receptors: serotonin 5HT_{2A/2C} (K_i=4 and 11 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM),
39 muscarinic M₁₋₅ (K_i=1.9-25 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors
40 (K_i=19 nM). Olanzapine binds weakly to GABA_A, BZD, and β adrenergic receptors (K_i>10 μM).

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

46 Antagonism at receptors other than dopamine and 5HT₂ with similar receptor affinities may
47 explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of
48 muscarinic M₁₋₅ receptors may explain its anticholinergic effects. Olanzapine's antagonism of
49 histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's
50 antagonism of adrenergic α₁ receptors may explain the orthostatic hypotension observed with this
51 drug.

52 Pharmacokinetics

53 Oral Administration

54 Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours
55 following an oral dose. It is eliminated extensively by first pass metabolism, with approximately
56 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the
57 rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets
58 and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are
59 bioequivalent.

60 Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to
61 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from
62 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

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

67 Olanzapine is extensively distributed throughout the body, with a volume of distribution of
68 approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to
69 1100 ng/mL, binding primarily to albumin and α₁-acid glycoprotein.

70 Metabolism and Elimination — Following a single oral dose of ¹⁴C labeled olanzapine, 7% of
71 the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine
72 is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and
73 feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total
74 radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major
75 circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the
76 concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the
77 concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations
78 observed.

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

84 **Intramuscular Administration**

85 ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations
86 occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a
87 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma
88 concentration approximately 5 times higher than the maximum plasma concentration produced
89 by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is
90 similar to that achieved after oral administration of the same dose. The half-life observed after
91 intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics
92 are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are
93 qualitatively similar to metabolic profiles after oral administration.

94 **Special Populations**

95 Renal Impairment — Because olanzapine is highly metabolized before excretion and only
96 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact
97 on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were
98 similar in patients with severe renal impairment and normal subjects, indicating that dosage
99 adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is
100 not removed by dialysis. The effect of renal impairment on metabolite elimination has not been
101 studied.

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

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

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

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

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

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

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

126 **Clinical Efficacy Data**

127 **Schizophrenia**

128 The efficacy of oral olanzapine in the treatment of schizophrenia was established in
129 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for
130 schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the

131 two trials, but this trial did not compare these two drugs on the full range of clinically relevant
132 doses for both.

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

146 (1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and
147 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to
148 placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis
149 cluster, on the PANSS Negative subscale, and on CGI Severity.

150 (2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine
151 (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, and 15.0 ± 2.5 mg/day) on a once daily schedule, the
152 two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were
153 superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the
154 highest olanzapine dose group was superior to placebo on the SANS. There was no clear
155 advantage for the high dose group over the medium dose group.

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

158 In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for
159 schizophrenia and who remained stable on olanzapine during open label treatment for at least
160 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to
161 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms
162 of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however,
163 criteria were met for stopping the trial early due to an excess of placebo relapses compared to
164 olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary
165 outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy
166 in patients stabilized for approximately 8 weeks and followed for an observation period of up to
167 8 months.

168 **Bipolar Disorder**

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

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

181 (1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine
 182 (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the
 183 reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with
 184 the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample
 185 size and site variability, was not shown to be superior to placebo on this outcome.

186 (2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine
 187 (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the
 188 reduction of Y-MRS total score.

189 (3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of
 190 bipolar disorder who had responded during an initial open-label treatment phase for about two
 191 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of
 192 olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse.
 193 Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and
 194 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response
 195 during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤ 12
 196 and HAM-D 21 to ≤ 8 . Relapse during the double-blind phase was defined as an increase of the
 197 Y-MRS or HAM-D 21 total score to ≥ 15 , or being hospitalized for either mania or depression. In
 198 the randomized phase, patients receiving continued olanzapine experienced a significantly longer
 199 time to relapse.

200 Combination Therapy — The efficacy of oral olanzapine with concomitant lithium or valproate
 201 in the treatment of acute manic episodes was established in two controlled trials in patients who
 202 met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials
 203 included patients with or without psychotic features and with or without a rapid-cycling course.
 204 The results of the trials follow:

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

211 (2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or
 212 valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥ 16) were
 213 randomized to receive either olanzapine or placebo, in combination with their original therapy.
 214 Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with
 215 lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 $\mu\text{g/mL}$ to
 216 125 $\mu\text{g/mL}$, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS
 217 total score.

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

219 The efficacy of intramuscular olanzapine for injection for the treatment of agitation was
 220 established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated
 221 inpatients from two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed
 222 episodes). Each of the trials included a single active comparator treatment arm of either
 223 haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study).
 224 Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically
 225 agitated and clinically appropriate candidates for treatment with intramuscular medication, and
 226 (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥ 14 on the five items
 227 comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor
 228 impulse control, tension, hostility, uncooperativeness and excitement items) with at least
 229 one individual item score ≥ 4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In
 230 the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging

231 from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of
 232 agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy
 233 measure used for assessing agitation signs and symptoms in these trials was the change from
 234 baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to
 235 three injections during the 24 hour IM treatment periods; however, patients could not receive the
 236 second injection until after the initial 2 hour period when the primary efficacy measure was
 237 assessed. The results of the trials follow:

238 (1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for
 239 schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg,
 240 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS
 241 Excited Component at 2 hours post-injection. However, the effect was larger and more consistent
 242 for the three highest doses. There were no significant pairwise differences for the 7.5 and 10 mg
 243 doses over the 5 mg dose.

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

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

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

255 INDICATIONS AND USAGE

256 Schizophrenia

257 Oral ZYPREXA is indicated for the treatment of schizophrenia.

258 The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of
 259 schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

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

266 Bipolar Disorder

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

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

273 Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with
 274 oral ZYPREXA after achieving a responder status for an average duration of two weeks was
 275 demonstrated in a controlled trial (*see* Clinical Efficacy Data *under* CLINICAL
 276 PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should
 277 periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see*
 278 DOSAGE AND ADMINISTRATION).

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

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

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

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

292 The efficacy of ZYPREXA IntraMuscular for the treatment of agitation associated with
293 schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled
294 trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes)
295 (*see* CLINICAL PHARMACOLOGY).

296 **CONTRAINDICATIONS**

297 ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

298 For specific information about the contraindications of lithium or valproate, refer to the
299 CONTRAINDICATIONS section of the package inserts for these other products.

300 **WARNINGS**

301 Hyperglycemia and Diabetes Mellitus — Hyperglycemia, in some cases extreme and associated
302 with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with
303 atypical antipsychotics including olanzapine. Assessment of the relationship between atypical
304 antipsychotic use and glucose abnormalities is complicated by the possibility of an increased
305 background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence
306 of diabetes mellitus in the general population. Given these confounders, the relationship between
307 atypical antipsychotic use and hyperglycemia-related adverse events is not completely
308 understood. However, epidemiological studies suggest an increased risk of treatment-emergent
309 hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise
310 risk estimates for hyperglycemia-related adverse events in patients treated with atypical
311 antipsychotics are not available.

312 Patients with an established diagnosis of diabetes mellitus who are started on atypical
313 antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk
314 factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment
315 with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of
316 treatment and periodically during treatment. Any patient treated with atypical antipsychotics
317 should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia,
318 and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical
319 antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has
320 resolved when the atypical antipsychotic was discontinued; however, some patients required
321 continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

322 Safety Experience in Elderly Patients with Dementia-Related Psychosis — In
323 placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the
324 incidence of death in olanzapine-treated patients was significantly greater than placebo-treated
325 patients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population to
326 increased mortality when treated with olanzapine include age >80 years, sedation, concomitant
327 use of benzodiazepines or presence of pulmonary conditions (e.g., pneumonia, with or without

328 aspiration). Olanzapine is not approved for the treatment of patients with dementia-related
329 psychosis.

330 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia —
331 Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were
332 reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In
333 placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse
334 events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine
335 is not approved for the treatment of patients with dementia-related psychosis.

336 Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes
337 referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with
338 administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are
339 hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability
340 (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional
341 signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute
342 renal failure.

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

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

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

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

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

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

372 Given these considerations, olanzapine should be prescribed in a manner that is most likely to
373 minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally
374 be reserved for patients (1) who suffer from a chronic illness that is known to respond to
375 antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful
376 treatments are not available or appropriate. In patients who do require chronic treatment, the

377 smallest dose and the shortest duration of treatment producing a satisfactory clinical response
378 should be sought. The need for continued treatment should be reassessed periodically.

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

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

384

PRECAUTIONS

385 General

386 Hemodynamic Effects — Olanzapine may induce orthostatic hypotension associated with
387 dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration
388 period, probably reflecting its α_1 -adrenergic antagonistic properties. Hypotension, bradycardia
389 with or without hypotension, tachycardia, and syncope were also reported during the clinical
390 trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in
391 non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular
392 olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered
393 4 hours apart), approximately one-third of these patients experienced a significant orthostatic
394 decrease in systolic blood pressure (i.e., decrease ≥ 30 mmHg) (*see* DOSAGE AND
395 ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in
396 phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with
397 agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in
398 phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus
399 pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on
400 intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of
401 hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to
402 psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

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

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

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

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

421 Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of
422 olanzapine-treated patients. There were confounding factors that may have contributed to the
423 occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients
424 with a history of seizures or with conditions that potentially lower the seizure threshold,

425 e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in
426 a population of 65 years or older.

427 Hyperprolactinemia — As with other drugs that antagonize dopamine D₂ receptors, olanzapine
428 elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue
429 culture experiments indicate that approximately one-third of human breast cancers are prolactin
430 dependent in vitro, a factor of potential importance if the prescription of these drugs is
431 contemplated in a patient with previously detected breast cancer of this type. Although
432 disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported
433 with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels
434 is unknown for most patients. As is common with compounds which increase prolactin release,
435 an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies
436 conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor
437 epidemiologic studies have shown an association between chronic administration of this class of
438 drugs and tumorigenesis in humans; the available evidence is considered too limited to be
439 conclusive.

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

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

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

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

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

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

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

471 Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic
472 drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with
473 advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used
474 cautiously in patients at risk for aspiration pneumonia.

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

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

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

487 In five placebo-controlled studies of olanzapine in elderly patients with dementia-related
488 psychosis (n=1184), the following treatment-emergent adverse events were reported in
489 olanzapine-treated patients at an incidence of at least 2% and significantly greater than
490 placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary
491 incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual
492 hallucinations. The rate of discontinuation due to adverse events was significantly greater with
493 olanzapine than placebo (13% vs 7%). As with other CNS-active drugs, olanzapine should be
494 used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment
495 of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with
496 dementia-related psychosis, vigilance should be exercised (*see* WARNINGS).

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

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

503 **Information for Patients**

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

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

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

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

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

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

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

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

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

525 **Laboratory Tests**

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

528 **Drug Interactions**

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

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

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

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

541 Charcoal — The administration of activated charcoal (1 g) reduced the C_{max} and AUC of oral
542 olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about
543 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

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

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

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

552 Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean
553 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in
554 olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the
555 overall variability between individuals, and therefore dose modification is not routinely
556 recommended.

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

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

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

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

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

576 Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active
577 metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics
578 of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the
579 co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic
580 hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the
581 pharmacokinetics of theophylline or its metabolites.

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

587 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

588 Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine
589 was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent
590 to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2,
591 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a
592 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,
593 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended
594 human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and
595 hemangiosarcomas was significantly increased in one mouse study in female mice dosed at
596 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m² basis).
597 These tumors were not increased in another mouse study in females dosed at 10 or
598 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m²
599 basis); in this study, there was a high incidence of early mortalities in males of the
600 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was
601 significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at
602 ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m²
603 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels
604 in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity
605 studies; however, measurements during subchronic toxicity studies showed that olanzapine
606 elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity
607 study. An increase in mammary gland neoplasms has been found in rodents after chronic
608 administration of other antipsychotic drugs and is considered to be prolactin mediated. The
609 relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is
610 unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

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

616 Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male
617 mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female
618 fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended
619 human daily oral dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment

620 reversed the effects on male mating performance. In female rats, the precoital period was
621 increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended
622 human daily oral dose on a mg/m² basis). Diestrus was prolonged and estrus delayed at
623 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis);
624 therefore olanzapine may produce a delay in ovulation.

625 **Pregnancy**

626 Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and
627 in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily
628 oral dose on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In an oral
629 rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed
630 at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a
631 mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended
632 human daily oral dose on a mg/m² basis). In an oral rabbit teratology study, fetal toxicity
633 (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic
634 dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m²
635 basis).

636 Placental transfer of olanzapine occurs in rat pups.

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

643 **Labor and Delivery**

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

646 **Nursing Mothers**

647 Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine
648 is excreted in human milk. It is recommended that women receiving olanzapine should not
649 breast-feed.

650 **Pediatric Use**

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

652 **Geriatric Use**

653 Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were
654 65 years of age or over. In patients with schizophrenia, there was no indication of any different
655 tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients
656 with dementia-related psychosis have suggested that there may be a different tolerability profile
657 in this population compared to younger patients with schizophrenia. As with other CNS-active
658 drugs, olanzapine should be used with caution in elderly patients with dementia. Olanzapine is
659 not approved for the treatment of patients with dementia-related psychosis. If the prescriber
660 elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised.
661 Also, the presence of factors that might decrease pharmacokinetic clearance or increase the
662 pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose
663 for any geriatric patient (*see* WARNINGS, PRECAUTIONS, and DOSAGE AND
664 ADMINISTRATION).

ADVERSE REACTIONS

665
666 The information below is derived from a clinical trial database for olanzapine consisting of
667 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and
668 722 patients with exposure to intramuscular olanzapine for injection. This database includes:
669 (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in
670 schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of
671 exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine
672 premarketing bipolar mania trials representing approximately 66 patient-years of exposure;
673 (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric
674 symptoms in association with Alzheimer's disease representing approximately 29 patient-years
675 of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of
676 December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for
677 injection premarketing trials in agitated patients with schizophrenia, Bipolar I Disorder (manic or
678 mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical
679 study database for olanzapine in combination with lithium or valproate, consisting of
680 224 patients who participated in bipolar mania trials with approximately 22 patient-years of
681 exposure, is included below.

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

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

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

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

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

713 **Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination**
714 **Trials**

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

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

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

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

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

730 **Adverse Events Associated with Discontinuation of Treatment in Short-Term**
731 **Combination Trials**

732 Bipolar Mania Combination Therapy — In a study of patients who were already tolerating
733 either lithium or valproate as monotherapy, discontinuation rates due to adverse events were
734 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for
735 patients who remained on lithium or valproate monotherapy. Discontinuations with the
736 combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient
737 were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

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

739 The most commonly observed adverse events associated with the use of oral olanzapine
740 (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated
741 patients (olanzapine incidence at least twice that for placebo) were:
742

Common Treatment-Emergent Adverse Events Associated with the 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

743 ¹ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
744

Common Treatment-Emergent Adverse Events Associated with the 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

745

746 There was one adverse event (somnolence) observed at an incidence of 5% or greater among
747 intramuscular olanzapine for injection-treated patients and not observed at an equivalent
748 incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo)
749 during the placebo-controlled premarketing studies. The incidence of somnolence during the
750 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar
751 mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

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

754 Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
755 adverse events that occurred in 2% or more of patients treated with oral olanzapine (doses
756 ≥ 2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of
757 placebo-controlled trials.

758

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

759 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
760 incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression,
761 diarrhea, dysmenorrhea², hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid
762 reaction, personality disorder³, rash, thinking abnormal, weight loss.

763 ² Denominator used was for females only (olanzapine, N=201; placebo, N=114).

764 ³ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

765

766 Commonly Observed Adverse Events in Short-Term Combination Trials

767 In the bipolar mania combination placebo-controlled trials, the most commonly observed
768 adverse events associated with the combination of olanzapine and lithium or valproate (incidence
769 of ≥5% and at least twice placebo) were:

770

Common Treatment-Emergent Adverse Events Associated with the 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

771

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

774 Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
775 adverse events that occurred in 2% or more of patients treated with the combination of
776 olanzapine (doses ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or
777 valproate alone who participated in the acute phase of placebo-controlled combination trials.
778

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

779 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
780 incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation,
781 akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence,
782 flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder², myalgia,
783 nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal,
784 vomiting.

785 ² Denominator used was for females only (olanzapine, N=128; placebo, N=51).
786

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

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

791 Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent
792 adverse events that occurred in 1% or more of patients treated with intramuscular olanzapine for
793 injection (dose range of 2.5-10.0 mg/injection) and with incidence greater than placebo who
794 participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or
795 bipolar mania.
796

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

797 ¹ Events reported by at least 1% of patients treated with olanzapine for injection, except the following events which
798 had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia,
799 nervousness.
800

801 **Additional Findings Observed in Clinical Trials**

802 The following findings are based on clinical trials.

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

804 Extrapyramidal Symptoms — The following table enumerates the percentage of patients with
805 treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal
806 rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at
807 3 fixed doses with placebo in the treatment of schizophrenia.
808

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL 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

809 * No statistically significant differences.

810 ¹ Percentage of patients with a Simpson-Angus Scale total score >3.

811 ² Percentage of patients with a Barnes Akathisia Scale global score ≥2.
812

813 The following table enumerates the percentage of patients with treatment-emergent
814 extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute
815 therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo
816 in the treatment of schizophrenia.
817

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL 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*

818 * Statistically significantly different from placebo.

819 ¹ Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck
820 rigidity, oculogyric crisis, opisthotonos, torticollis.

821 ² Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity,
822 extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

823 ³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

824 ⁴ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome,
825 choreoathetosis, dyskinesia, tardive dyskinesia.

826 ⁵ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus,
827 twitching.

828

829 The following table enumerates the percentage of patients with treatment-emergent
830 extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during
831 controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with
832 placebo in agitation. Patients in each dose group could receive up to three injections during the
833 trials (*see CLINICAL PHARMACOLOGY*). Patient assessments were conducted during the
834 24 hours following the initial dose of intramuscular olanzapine for injection. There were no
835 statistically significant differences from placebo.

836

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSE, PLACEBO-CONTROLLED CLINICAL TRIAL OF INTRAMUSCULAR OLANZAPINE FOR INJECTION 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

837 * No statistically significant differences.

838 ¹ Percentage of patients with a Simpson-Angus total score >3.

839 ² Percentage of patients with a Barnes Akathisia Scale global score ≥2.

840

841 The following table enumerates the percentage of patients with treatment-emergent
842 extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same
843 controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with

844 placebo in agitated patients with schizophrenia. There were no statistically significant differences
845 from placebo.

846

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE
EVENTS INCIDENCE IN A FIXED DOSE, PLACEBO-CONTROLLED CLINICAL TRIAL
OF INTRAMUSCULAR OLANZAPINE FOR INJECTION 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

847 * No statistically significant differences.

848 ¹ Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck
849 rigidity, oculogyric crisis, opisthotonos, torticollis.

850 ² Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity,
851 extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

852 ³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

853 ⁴ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome,
854 choreoathetosis, dyskinesia, tardive dyskinesia.

855 ⁵ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus,
856 twitching.

857

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

864

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

865

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

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

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

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

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

896 **Other Adverse Events Observed During the Clinical Trial Evaluation of** 897 **Olanzapine**

898 Following is a list of terms that reflect treatment-emergent adverse events reported by patients
899 treated with oral olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials (8661 patients,
900 4165 patient-years of exposure). This listing may not include those events already listed in
901 previous tables or elsewhere in labeling, those events for which a drug cause was remote, those
902 event terms which were so general as to be uninformative, and those events reported only once or
903 twice which did not have a substantial probability of being acutely life-threatening.

904 Events are further categorized by body system and listed in order of decreasing frequency
905 according to the following definitions: frequent adverse events are those occurring in at least
906 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
907 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients;
908 rare events are those occurring in fewer than 1/1000 patients.

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

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

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

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

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

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

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

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

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

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

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

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

952 **Urogenital System** — *Frequent*: vaginitis*; *Infrequent*: abnormal ejaculation*, amenorrhea*,
 953 breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria,
 954 gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*,
 955 polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency,
 956 urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare*: albuminuria,
 957 breast enlargement, mastitis, and oliguria.

958 * Adjusted for gender.

959

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

966 Events are further categorized by body system and listed in order of decreasing frequency
 967 according to the following definitions: frequent adverse events are those occurring in at least

968 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
969 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

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

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

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

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

974 **Metabolic and Nutritional Disorders** — *Infrequent*: creatine phosphokinase increased,
975 dehydration, and hyperkalemia.

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

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

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

980 **Postintroduction Reports**

981 Adverse events reported since market introduction that were temporally (but not necessarily
982 causally) related to ZYPREXA therapy include the following: allergic reaction
983 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis,
984 priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism
985 and deep venous thrombosis).

986 **DRUG ABUSE AND DEPENDENCE**

987 **Controlled Substance Class**

988 Olanzapine is not a controlled substance.

989 **Physical and Psychological Dependence**

990 In studies prospectively designed to assess abuse and dependence potential, olanzapine was
991 shown to have acute depressive CNS effects but little or no potential of abuse or physical
992 dependence in rats administered oral doses up to 15 times the maximum recommended human
993 daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum
994 recommended human daily oral dose on a mg/m² basis.

995 Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance,
996 or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking
997 behavior, these observations were not systematic, and it is not possible to predict on the basis of
998 this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or
999 abused once marketed. Consequently, patients should be evaluated carefully for a history of drug
1000 abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine
1001 (e.g., development of tolerance, increases in dose, drug-seeking behavior).

1002 **OVERDOSAGE**

1003 **Human Experience**

1004 In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or
1005 intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the
1006 largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred
1007 speech. In the limited number of patients who were evaluated in hospitals, including the patient
1008 taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or
1009 ECG. Vital signs were usually within normal limits following overdoses.

1010 In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in
1011 the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included
1012 agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced
1013 level of consciousness ranging from sedation to coma. Among less commonly reported

1014 symptoms were the following potentially medically serious events: aspiration, cardiopulmonary
 1015 arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing
 1016 sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic
 1017 malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension.
 1018 Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine
 1019 alone. In one case of death, the amount of acutely ingested olanzapine was reported to be
 1020 possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute
 1021 olanzapine ingestion of 1500 mg.

1022 **Overdosage Management**

1023 The possibility of multiple drug involvement should be considered. In case of acute
 1024 overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation,
 1025 which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and
 1026 administration of activated charcoal together with a laxative should be considered. The
 1027 possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose
 1028 may create a risk of aspiration with induced emesis. Cardiovascular monitoring should
 1029 commence immediately and should include continuous electrocardiographic monitoring to detect
 1030 possible arrhythmias.

1031 There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should
 1032 be initiated. Hypotension and circulatory collapse should be treated with appropriate measures
 1033 such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine,
 1034 or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen
 1035 hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and
 1036 monitoring should continue until the patient recovers.

1037 **DOSAGE AND ADMINISTRATION**

1038 **Schizophrenia**

1039 Usual Dose — Oral olanzapine should be administered on a once-a-day schedule without
 1040 regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day
 1041 within several days. Further dosage adjustments, if indicated, should generally occur at intervals
 1042 of not less than 1 week, since steady state for olanzapine would not be achieved for
 1043 approximately 1 week in the typical patient. When dosage adjustments are necessary, dose
 1044 increments/decrements of 5 mg QD are recommended.

1045 Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical
 1046 trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the
 1047 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of
 1048 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above
 1049 20 mg/day has not been evaluated in clinical trials.

1050 Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are
 1051 debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a
 1052 combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking
 1053 female patients ≥ 65 years of age), or who may be more pharmacodynamically sensitive to
 1054 olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant
 1055 Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should
 1056 be performed with caution in these patients.

1057 Maintenance Treatment — While there is no body of evidence available to answer the question
 1058 of how long the patient treated with olanzapine should remain on it, the effectiveness of oral
 1059 olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients
 1060 who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a
 1061 period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL

1062 PHARMACOLOGY). Patients should be periodically reassessed to determine the need for
1063 maintenance treatment with appropriate dose.

1064 **Bipolar Disorder**

1065 Usual Monotherapy Dose — Oral olanzapine should be administered on a once-a-day schedule
1066 without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated,
1067 should generally occur at intervals of not less than 24 hours, reflecting the procedures in the
1068 placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements
1069 of 5 mg QD are recommended.

1070 Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
1071 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
1072 clinical trials.

1073 Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with
1074 oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average
1075 duration of two weeks, was demonstrated in a controlled trial (*see Clinical Efficacy Data under*
1076 **CLINICAL PHARMACOLOGY**). The physician who elects to use ZYPREXA for extended
1077 periods should periodically re-evaluate the long-term usefulness of the drug for the individual
1078 patient.

1079 Bipolar Mania Usual Dose in Combination with Lithium or Valproate — When administered
1080 in combination with lithium or valproate, oral olanzapine dosing should generally begin with
1081 10 mg once-a-day without regard to meals.

1082 Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
1083 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
1084 clinical trials.

1085 Dosing in Special Populations — *See Dosing in Special Populations under DOSAGE AND*
1086 *ADMINISTRATION, Schizophrenia.*

1087 *Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)*

1088 After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately
1089 upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in
1090 the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or
1091 without liquid.

1092 **Agitation Associated with Schizophrenia and Bipolar I Mania**

1093 Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania — The efficacy of
1094 intramuscular olanzapine for injection in controlling agitation in these disorders was
1095 demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is
1096 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (*see*
1097 **CLINICAL PHARMACOLOGY**). If agitation warranting additional intramuscular doses persists
1098 following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of
1099 repeated doses of intramuscular olanzapine for injection in agitated patients has not been
1100 systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater
1101 than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and
1102 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of
1103 intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be
1104 associated with a substantial occurrence of significant orthostatic hypotension (*see*
1105 **PRECAUTIONS, Hemodynamic Effects**). Thus, it is recommended that patients requiring
1106 subsequent intramuscular injections be assessed for orthostatic hypotension prior to the
1107 administration of any subsequent doses of intramuscular olanzapine for injection. The
1108 administration of an additional dose to a patient with a clinically significant postural change in
1109 systolic blood pressure is not recommended.

1110 If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range
 1111 of 5-20 mg/day as soon as clinically appropriate (*see* Schizophrenia or Bipolar Disorder *under*
 1112 DOSAGE AND ADMINISTRATION).

1113 Intramuscular Dosing in Special Populations — A dose of 5 mg per injection should be
 1114 considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg
 1115 per injection should be considered for patients who otherwise might be debilitated, be
 1116 predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine
 1117 (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and
 1118 Drug Interactions *under* PRECAUTIONS).

1119 Administration of ZYPREXA IntraMuscular

1120 ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer
 1121 intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

1122 Parenteral drug products should be inspected visually for particulate matter and discoloration
 1123 prior to administration, whenever solution and container permit.

1124 Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection

1125 Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a
 1126 solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear
 1127 clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should
 1128 be used immediately (within 1 hour) after reconstitution. **Discard any unused portion.**

1129 The following table provides injection volumes for delivering various doses of intramuscular
 1130 olanzapine for injection reconstituted with Sterile Water for Injection.

1131

<u>Dose, mg Olanzapine</u>	<u>Volume of Injection, mL</u>
10.0	Withdraw total contents of vial
7.5	1.5
5.0	1.0
2.5	0.5

1132

1133 Physical Incompatibility Information

1134 ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection.
 1135 ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because
 1136 precipitation occurs when these products are mixed. Lorazepam injection should not be used to
 1137 reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution
 1138 time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection
 1139 because the resulting low pH has been shown to degrade olanzapine over time.

1140

HOW SUPPLIED

1141 The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in
 1142 blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with
 1143 LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and
 1144 tablet number. The tablets are available as follows:

1145

	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	LILLY	LILLY	LILLY	LILLY	LILLY
NDC Codes:	4112	4115	4116	4117	4415	4420

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

1146 * Identi-Dose® (unit dose medication, Lilly).
1147

1148 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed
1149 with the tablet strength. The tablets are available as follows:
1150

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

1151
1152 ZYPREXA is a registered trademark of Eli Lilly and Company.
1153 ZYDIS is a registered trademark of Cardinal Health, Inc. or one of its subsidiaries.
1154 *ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and
1155 Company by Cardinal Health, United Kingdom, SN5 8RU.
1156

1157 ZYPREXA IntraMuscular is available in:
1158 NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)
1159

1160 Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before
1161 reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].
1162 Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature,
1163 20° to 25°C (68° to 77°F) [see USP] for up to 1 hour if necessary. **Discard any unused portion**
1164 **of reconstituted ZYPREXA IntraMuscular.** The USP defines controlled room temperature as
1165 a temperature maintained thermostatically that encompasses the usual and customary working
1166 environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to
1167 be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that
1168 are experienced in pharmacies, hospitals, and warehouses.

1169 Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect
1170 ZYPREXA IntraMuscular from light, do not freeze.

1171 ANIMAL TOXICOLOGY

1172 In animal studies with olanzapine, the principal hematologic findings were reversible
1173 peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum
1174 recommended human daily oral dose on a mg/m² basis), dose-related decreases in lymphocytes
1175 and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed
1176 reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of
1177 treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses
1178 of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m²
1179 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased
1180 body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended

1181 human daily oral dose on a mg/m² basis) for 3 months or 16 mg/kg (8 times the maximum
1182 recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone
1183 marrow cytotoxicity was found in any of the species examined. Bone marrows were
1184 normocellular or hypercellular, indicating that the reductions in circulating blood cells were
1185 probably due to peripheral (non-marrow) factors.

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