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ZYPREXA[®] (Olanzapine) Tablets

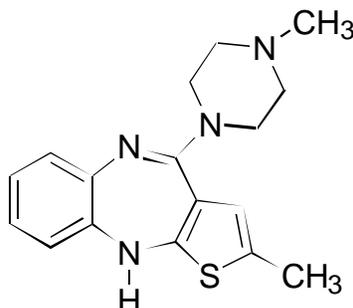
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ZYPREXA[®] ZYDIS[®] (Olanzapine) Orally Disintegrating Tablets

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DESCRIPTION

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



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

13 ZYPREXA tablets are intended for oral administration only.

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

21 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration
22 only.

23 Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg
24 (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within
25 seconds, allowing its contents to be subsequently swallowed with or without liquid.

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

28

CLINICAL PHARMACOLOGY

29

Pharmacodynamics

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

34 The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is
35 unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated
36 through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. The mechanism of

37 action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is
38 unknown.

39 Antagonism at receptors other than dopamine and 5HT₂ with similar receptor affinities may
40 explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of
41 muscarinic M₁₋₅ receptors may explain its anticholinergic effects. Olanzapine's antagonism of
42 histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's
43 antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this
44 drug.

45 **Pharmacokinetics**

46 Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours
47 following an oral dose. It is eliminated extensively by first pass metabolism, with approximately
48 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the
49 rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets
50 and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are
51 bioequivalent.

52 Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to
53 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to
54 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

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

59 Olanzapine is extensively distributed throughout the body, with a volume of distribution of
60 approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to
61 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

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

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

76 **Special Populations**

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

83 Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce
84 the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with

85 clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the
86 pharmacokinetics of olanzapine.

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

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

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

97 Race — No specific pharmacokinetic study was conducted to investigate the effects of race. A
98 cross-study comparison between data obtained in Japan and data obtained in the US suggests that
99 exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are
100 administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant
101 differences among Caucasian patients, patients of African descent, and a third pooled category
102 including Asian and Hispanic patients. Dosage modifications for race are, therefore, not
103 recommended.

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

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

111 **Clinical Efficacy Data**

112 **Schizophrenia**

113 The efficacy of olanzapine in the treatment of schizophrenia was established in 2 short-term
114 (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A
115 single haloperidol arm was included as a comparative treatment in one of the two trials, but this
116 trial did not compare these two drugs on the full range of clinically relevant doses for both.

117 Several instruments were used for assessing psychiatric signs and symptoms in these studies,
118 among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general
119 psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The
120 BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and
121 unusual thought content) is considered a particularly useful subset for assessing actively psychotic
122 schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI),
123 reflects the impression of a skilled observer, fully familiar with the manifestations of
124 schizophrenia, about the overall clinical state of the patient. In addition, two more recently
125 developed but less well evaluated scales were employed; these included the 30-item Positive and
126 Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the
127 Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the
128 following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative
129 subscale or SANS; and CGI Severity. The results of the trials follow:

130 (1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and
131 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to
132 placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis
133 cluster, on the PANSS Negative subscale, and on CGI Severity.

134 (2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine
135 (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
136 two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were
137 superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the
138 highest olanzapine dose group was superior to placebo on the SANS. There was no clear
139 advantage for the high dose group over the medium dose group.

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

142 In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for
143 schizophrenia and who remained stable on olanzapine during open label treatment for at least
144 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to
145 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms
146 of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however,
147 criteria were met for stopping the trial early due to an excess of placebo relapses compared to
148 olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary
149 outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in
150 patients stabilized for approximately 8 weeks and followed for an observation period of up to
151 8 months.

152 **Bipolar Mania**

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

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

164 (1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine
165 (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the
166 reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the
167 first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size
168 and site variability, was not shown to be superior to placebo on this outcome.

169 (2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine
170 (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the
171 reduction of Y-MRS total score.

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

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

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

189

INDICATIONS AND USAGE

190 **Schizophrenia**

191 ZYPREXA is indicated for the treatment of schizophrenia.

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

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

200 **Bipolar Mania**

201 Monotherapy — ZYPREXA is indicated for the short-term treatment of acute manic episodes
202 associated with Bipolar I Disorder.

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

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

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

213 The effectiveness of ZYPREXA for longer-term use, that is, for more than 6 weeks' treatment of
214 an acute episode, and for prophylactic use in mania, has not been systematically evaluated in
215 controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods
216 should periodically re-evaluate the long-term risks and benefits of the drug for the individual
217 patient (*see* DOSAGE AND ADMINISTRATION).

218

CONTRAINDICATIONS

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

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

222

WARNINGS

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

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

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

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

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

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

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

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

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

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

271

PRECAUTIONS

272 **General**

273 Orthostatic Hypotension — Olanzapine may induce orthostatic hypotension associated with
274 dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration
275 period, probably reflecting its α_1 -adrenergic antagonistic properties. Syncope was reported in
276 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic
277 hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE
278 AND ADMINISTRATION). A more gradual titration to the target dose should be considered if

279 hypotension occurs. Olanzapine should be used with particular caution in patients with known
280 cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction
281 abnormalities), cerebrovascular disease, and conditions which would predispose patients to
282 hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

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

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

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

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

314 Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to
315 transaminase increases.

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

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

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

327 Body Temperature Regulation — Disruption of the body's ability to reduce core body
328 temperature has been attributed to antipsychotic agents. Appropriate care is advised when

329 prescribing olanzapine for patients who will be experiencing conditions which may contribute to
330 an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat,
331 receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

332 Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic
333 drug use. Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's
334 disease died from aspiration pneumonia during or within 30 days of the termination of the
335 double-blind portion of their respective studies; there were no deaths in the placebo-treated
336 patients. One of these patients had experienced dysphagia prior to the development of aspiration
337 pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with
338 advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used
339 cautiously in patients at risk for aspiration pneumonia.

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

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

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

352 In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in
353 nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State
354 Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with
355 Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each
356 and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of
357 the placebo-treated group, where at least 1 placebo-treated patient was reported to have
358 experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have
359 experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of
360 discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to
361 abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs
362 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be
363 drug related. As with other CNS-active drugs, olanzapine should be used with caution in elderly
364 patients with dementia (*see* PRECAUTIONS).

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

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

371 **Information for Patients**

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

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

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

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

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

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

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

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

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

393 **Laboratory Tests**

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

396 **Drug Interactions**

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

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

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

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

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

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

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

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

420 Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean
421 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in
422 olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the
423 overall variability between individuals, and therefore dose modification is not routinely
424 recommended.

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

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

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

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

438 Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little
439 potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate
440 has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine
441 (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate.
442 Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

443 Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active
444 metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics
445 of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the
446 co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic
447 hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the
448 pharmacokinetics of theophylline or its metabolites.

449 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

450 Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine
451 was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent
452 to 0.8-5 times the maximum recommended human daily dose on a mg/m² basis) and 0.25, 2,
453 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m²
454 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4,
455 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human
456 daily dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and
457 hemangiosarcomas was significantly increased in one mouse study in female mice dosed at
458 8 mg/kg/day (2 times the maximum recommended human daily dose on a mg/m² basis). These
459 tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day
460 (2-5 times the maximum recommended human daily dose on a mg/m² basis); in this study, there
461 was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of
462 mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed
463 at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum
464 recommended human daily dose on a mg/m² basis, respectively). Antipsychotic drugs have been
465 shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not
466 measured during the olanzapine carcinogenicity studies; however, measurements during subchronic
467 toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the
468 same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been
469 found in rodents after chronic administration of other antipsychotic drugs and is considered to be
470 prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine
471 tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

472 Mutagenesis — No evidence of mutagenic potential for olanzapine was found in the Ames
473 reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in

474 Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of
475 forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone
476 marrow of Chinese hamsters.

477 **Impairment of Fertility** — In a fertility and reproductive performance study in rats, male mating
478 performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was
479 decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily
480 dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects
481 on male mating performance. In female rats, the precoital period was increased and the mating
482 index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily dose on a mg/m²
483 basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum
484 recommended human daily dose on a mg/m² basis); therefore olanzapine may produce a delay in
485 ovulation.

486 **Pregnancy**

487 **Pregnancy Category C** — In reproduction studies in rats at doses up to 18 mg/kg/day and in
488 rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily dose
489 on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In a rat teratology
490 study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of
491 18 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m² basis). Gestation
492 was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m²
493 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and
494 decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the
495 maximum recommended human daily dose on a mg/m² basis).

496 Placental transfer of olanzapine occurs in rat pups.

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

503 **Labor and Delivery**

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

506 **Nursing Mothers**

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

510 **Pediatric Use**

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

512 **Geriatric Use**

513 Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years
514 of age or over. In patients with schizophrenia, there was no indication of any different tolerability
515 of olanzapine in the elderly compared to younger patients. Studies in patients with various
516 psychiatric symptoms in association with Alzheimer's disease have suggested that there may be a
517 different tolerability profile in this population compared to younger patients with schizophrenia.
518 As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with
519 dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase

520 the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose
521 for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

522 **ADVERSE REACTIONS**

523 The information below is derived from a clinical trial database for olanzapine consisting of
524 4189 patients with approximately 2665 patient-years of exposure. This database includes:
525 (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and
526 Alzheimer's disease representing approximately 1122 patient-years of exposure as of
527 February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials
528 representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a
529 trial of patients having various psychiatric symptoms in association with Alzheimer's disease
530 representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional
531 clinical trials as of May 1, 1997. In addition, information from the premarketing 6-week clinical
532 study database for olanzapine in combination with lithium or valproate, consisting of 224 patients
533 who participated in bipolar mania trials with approximately 22 patient-years of exposure, is
534 included below.

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

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

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

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

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

565 **Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination**
 566 **Trials**

567 The following findings are based on premarketing trials for schizophrenia, bipolar mania, a
 568 subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's
 569 disease, and premarketing combination trials.

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

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

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

578 **Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination**
 579 **Trials**

580 Bipolar Mania Combination Therapy — In a study of patients who were already tolerating either
 581 lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the
 582 combination of olanzapine with lithium or valproate compared to 2% for patients who **remained on**
 583 lithium or valproate monotherapy. Discontinuations with the combination of olanzapine and lithium
 584 or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and
 585 peripheral edema (1%).
 586

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

588 The most commonly observed adverse events associated with the use of olanzapine (incidence
 589 of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients
 590 (olanzapine incidence at least twice that for placebo) were:
 591

Common Treatment-Emergent Adverse Events Associated with the Use of 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

592 ¹ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
 593

Common Treatment-Emergent Adverse Events Associated with the Use of 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

594

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

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

601

Table 1
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials¹
Percentage of Patients Reporting Event

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

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

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

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

608

609 Commonly Observed Adverse Events in Short-Term Combination Trials

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

613

Common Treatment-Emergent Adverse Events Associated with the Use of 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

614

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

617 Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse
618 events that occurred in 2% or more of patients treated with the combination of olanzapine (doses
619 ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone
620 who participated in the acute phase of placebo-controlled combination trials.

621

Table 2
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials¹

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

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

628 ² Denominator used was for females only (olanzapine, N=128; placebo, N=51).
629

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

632 **Additional Findings Observed in Clinical Trials**

633 The following findings are based on clinical trials.

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

635 Extrapyramidal Symptoms — The following table enumerates the percentage of patients with
636 treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating
637 scales during acute therapy in a controlled clinical trial comparing olanzapine at 3 fixed doses
638 with placebo in the treatment of schizophrenia.
639

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

* No statistically significant differences.

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

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

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

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

* Statistically significantly different from placebo.

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

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

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

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

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

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

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

667

668 *Vital Sign Changes* — Olanzapine is associated with orthostatic hypotension and tachycardia
669 (*see* PRECAUTIONS).

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

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

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

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

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

698 Following is a list of terms that reflect treatment-emergent adverse events reported by patients
699 treated with olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials (4189 patients,
700 2665 patient-years of exposure). This listing does not include those events already listed in
701 previous tables or elsewhere in labeling, those events for which a drug cause was remote, those
702 event terms which were so general as to be uninformative, and those events reported only once
703 which did not have a substantial probability of being acutely life-threatening.

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

706 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
707 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients;
708 rare events are those occurring in fewer than 1/1000 patients.

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

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

717 **Digestive System** — *Frequent*: increased salivation and thirst; *Infrequent*: dysphagia,
718 eructation, fecal impaction, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis,
719 hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess,
720 rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare*: aphthous stomatitis, enteritis,
721 esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue
722 discoloration.

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

724 **Hemic and Lymphatic System** — *Frequent*: leukopenia; *Infrequent*: anemia, cyanosis,
725 leukocytosis, lymphadenopathy, thrombocythemia, and thrombocytopenia; *Rare*: normocytic
726 anemia.

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

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

734 **Nervous System** — *Frequent*: abnormal dreams, emotional lability, euphoria, libido
735 decreased, paresthesia, and schizophrenic reaction; *Infrequent*: alcohol misuse, amnesia,
736 antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, coma, delirium, depersonalization,
737 dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased,
738 obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering,
739 tardive dyskinesia, tobacco misuse, vertigo, and withdrawal syndrome; *Rare*: akinesia, circumoral
740 paresthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, and subarachnoid
741 hemorrhage.

742 **Respiratory System** — *Frequent*: dyspnea; *Infrequent*: apnea, aspiration pneumonia, asthma,
743 atelectasis, epistaxis, hemoptysis, hyperventilation, laryngitis, pneumonia, and voice alteration;
744 *Rare*: hiccup, hypoventilation, hypoxia, lung edema, and stridor.

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

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

752 **Urogenital System** — *Frequent*: amenorrhea*, hematuria, metrorrhagia*, and vaginitis*;
753 *Infrequent*: abnormal ejaculation*, breast pain, cystitis, decreased menstruation*, dysuria, female
754 lactation, glycosuria, impotence*, increased menstruation*, menorrhagia*, polyuria, premenstrual

755 syndrome*, pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids
 756 enlarged*, and vaginal hemorrhage*; *Rare*: albuminuria, gynecomastia, mastitis, oliguria, and
 757 urinary urgency.

758 *Adjusted for gender.

759 **Postintroduction Reports**

760 Adverse events reported since market introduction which were temporally (but not necessarily
 761 causally) related to ZYPREXA therapy include the following: allergic reaction
 762 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, and
 763 priapism.

764 **DRUG ABUSE AND DEPENDENCE**

765 **Controlled Substance Class**

766 Olanzapine is not a controlled substance.

767 **Physical and Psychological Dependence**

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

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

780 **OVERDOSAGE**

781 **Human Experience**

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

788 During the first 2 years of marketing, Eli Lilly and Company received reports of 178 cases of
 789 possible or definite overdose with olanzapine alone (at doses up to 1500 mg). Symptoms possibly
 790 but not necessarily causally attributable to the overdose were reported in 76% of these cases
 791 while 24% of reported cases had no symptoms attributable to overdose. In symptomatic patients,
 792 symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia,
 793 various extrapyramidal symptoms, and reduced level of consciousness. Among less commonly
 794 reported symptoms were the following potentially medically serious events: aspiration,
 795 cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient
 796 experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible
 797 neuroleptic malignant syndrome, coma, respiratory depression/arrest, convulsion, hypertension,
 798 and hypotension. Eli Lilly and Company has received reports of fatality in association with
 799 overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was
 800 reported to be possibly as low as 450 mg; however, in another case, a patient was reported to
 801 survive an acute olanzapine ingestion of 1500 mg.

802 **Overdosage Management**

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

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

816 **DOSAGE AND ADMINISTRATION**

817 **Schizophrenia**

818 Usual Dose — Olanzapine should be administered on a once-a-day schedule without regard to
819 meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within
820 several days. Further dosage adjustments, if indicated, should generally occur at intervals of not
821 less than 1 week, since steady state for olanzapine would not be achieved for approximately
822 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements
823 of 5 mg QD are recommended.

824 Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials.
825 However, doses above 10 mg/day were not demonstrated to be more efficacious than the
826 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of
827 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above
828 20 mg/day has not been evaluated in clinical trials.

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

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

843 **Bipolar Mania**

844 Usual Monotherapy Dose — Olanzapine should be administered on a once-a-day schedule
845 without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated,
846 should generally occur at intervals of not less than 24 hours, reflecting the procedures in the
847 placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of
848 5 mg QD are recommended.

849 Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
850 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
851 clinical trials.

852 Usual Dose in Combination with Lithium or Valproate — When administered in combination
853 with lithium or valproate, olanzapine dosing should generally begin with 10 mg once-a-day
854 without regard to meals.

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

857 Dosing in Special Populations — See Dosing in Special Populations *under* DOSAGE AND
858 ADMINISTRATION, Schizophrenia.

859 Maintenance Treatment — There is no body of evidence available from controlled trials to
860 guide a clinician in the longer-term management of a patient who improves during treatment of an
861 acute manic episode with olanzapine. While it is generally agreed that pharmacological treatment
862 beyond an acute response in mania is desirable, both for maintenance of the initial response and
863 for prevention of new manic episodes, there are no systematically obtained data to support the use
864 of olanzapine in such longer-term treatment (i.e., beyond 6 weeks).

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

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

870 HOW SUPPLIED

871 The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue
872 ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with
873 LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and
874 tablet number. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 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

876 * Identi-Dose[®] (unit dose medication, Lilly).

877

878 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed
 879 with the tablet strength. The tablets are available as follows:
 880

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

881

882 ZYPREXA is a registered trademark of Eli Lilly and Company.

883 ZYDIS is a registered trademark of R. P. Scherer Corporation.

884 *ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and
 885 Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

886 Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. The USP defines
 887 controlled room temperature as a temperature maintained thermostatically that encompasses the
 888 usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean
 889 kinetic temperature calculated to be not more than 25°C; and that allows for excursions between
 890 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

891 Protect from light and moisture.

892

ANIMAL TOXICOLOGY

893 In animal studies with olanzapine, the principal hematologic findings were reversible peripheral
 894 cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human
 895 daily dose on a mg/m² basis), dose-related decreases in lymphocytes and neutrophils in mice, and
 896 lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or
 897 reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in
 898 lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the
 899 maximum recommended human daily dose on a mg/m² basis) in studies of 3 months' duration.
 900 Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving
 901 22.5 mg/kg (11 times the maximum recommended human daily dose on a mg/m² basis) for 3 months
 902 or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m² basis) for 6 or
 903 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined.
 904 Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating
 905 blood cells were probably due to peripheral (non-marrow) factors.

906 Literature revised Month dd, 2003

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