

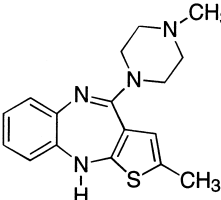
ZYPREXA® (Olanzapine) Tablets

ZYPREXA® ZYDIS® (Olanzapine) Orally Disintegrating Tablets

PV 3399 AMP

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



Olanzapine is a yellow crystalline solid, which is practically insoluble in water. ZYPREXA tablets are intended for oral administration. Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, croscopolone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2, Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with a white ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only. Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT_{2A/2C} (K_d 4 and 11 nM, respectively), dopamine D₁₋₄ (K_d 11-31 nM), muscarinic M₁₋₅ (K_d 1.9-25 nM), histamine H₁ (K_d 7 nM) and α₁ adrenergic α₁ receptors (K_d 19 nM). Olanzapine binds weakly to GABA_A, β_{2D}, and β₃ adrenergic receptors (K_d 10-100 nM).

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

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

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

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

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

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

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

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

Special Populations

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

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

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

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

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

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

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. A more recently developed but less well evaluated scales were employed; these included the Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

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

Clinical Efficacy Data

Schizophrenia

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

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

(1) In a 6-week placebo-controlled trial (n=159) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS negative subscale, and on CGI Severity.

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

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

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

Bipolar Mania

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

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

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

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

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

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

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

INDICATIONS AND USAGE

Schizophrenia

ZYPREXA is indicated for the treatment of schizophrenia. The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

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

Bipolar Mania

Monotherapy — ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder. The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

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

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features. The patient should be carefully monitored, since recurrences of NMS have been reported.

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

CONTRAINDICATIONS

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

WARNINGS

Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been associated with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

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

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

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

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Persistent and new cases of tardive dyskinesia, particularly those attributable to olanzapine, should be considered if hypokinesia or akinesia that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be periodically re-evaluated.

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

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

PRECAUTIONS

General

Orthostatic Hypotension — Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α₁-adrenergic antagonistic properties. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (see DOSAGE AND ADMINISTRATION). Orthostatic hypotension should be considered if hypotension occurs. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

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

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

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

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

Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases. Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Laboratory Tests).

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

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

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

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

Suicide — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients is advised. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

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

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

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

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

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

Information for Patients

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

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

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

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

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

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

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

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

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

Laboratory Tests

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

Drug Interactions

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

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Effect of Olanzapine on Other Drugs — Agents that inhibit CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may be necessary in patients receiving these enzyme-affecting drugs.

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

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

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

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

Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 10%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC was 108% and 103%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

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

Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Thus, olanzapine is unlikely to cause clinically important drug-drug interactions mediated by these enzymes.

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

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

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam in rats. In addition, co-administration of either diazepam or N-desmethyldiazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites

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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

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

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

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

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

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

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	4
Constipation	9	5
Dyspepsia	7	4
Vomiting	4	3
Increased appetite	4	2
Hemic and Lymphatic System		
Echymosis	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

¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dyspareunia², hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder³, rash, thinking abnormal, weight loss.
² Denominator used was for females only (olanzapine, N=201; placebo, N=114).
³ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Commonly Observed Adverse Events in Short-Term Combination Trials

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

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

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

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

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

¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abnormal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, dyspepsia, emotional lability, fever, flatulence, flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder², myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.
² Denominator used was for females only (olanzapine, N=128; placebo, N=51).

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

Additional Findings Observed in Clinical Trials

The following findings are based on clinical trials.

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

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

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL — ACUTE PHASE¹

	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)
Parkinsonism ¹	15	14	12	14
Akathisia ²	23	16	19	27

¹ No statistically significant differences.
² Percentage of patients with a Simpson-Angus Scale total score >3.
³ 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*

¹ Statistically significantly different from placebo.
² Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonus, torticollis.
³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia, cogwheel rigidity, extrapyramidal syndrome, hypertension, hypokinesia, masked faces, tremor.
⁴ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
⁵ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
⁶ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

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

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 dosage ranges 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	Placebo (N=69)	Percentage of Patients Reporting Event		
		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

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

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

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

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

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

Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses ≥1 mg/day) in clinical trials (4159 patients, 2665 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

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

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

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

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

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

Hemic and Lymphatic System — *Frequent:* leukopenia; *Infrequent:* anemia, cyanosis, leukocytosis, lymphadenopathy, thrombocytopenia, and thrombocytopenia; *Rare:* necrotic anemia.

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

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

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

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

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

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

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

*Adjusted for gender.

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
Olanzapine is not a controlled substance.

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

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

OVERDOSAGE

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

During the first year of marketing, Eli Lilly and Company received reports of 178 cases of possibly or definite overdose with olanzapine alone (at doses up to 1500 mg). Symptoms possibly but not necessarily causally attributable to the overdose were reported in 76% of these cases while 24% of reported cases had no symptoms attributable to overdose. In symptomatic patients, symptoms with >10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, coma, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of 1 fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

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

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

DOSAGE AND ADMINISTRATION

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

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

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

Maintenance Treatment — While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 5 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

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

Short-term (3-4 weeks) antimanic