PCP Discussion Guide

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Lilly

Discussion Guide

In our discussion this evening, we will discuss:

- Patients who exhibit complicated mood symptoms associated with bipolar mania including *irritability, anxiety, disrupted sleep, and mood swings*
- Current treatment plans and results thus far. Are you frustrated about these patients? What symptoms are you trying to alleviate?
- Using ZYPREXA® (olanzapine) for patients with complicated mood symptoms

File name location
2

Profile: Ashley

- Ashley is a 42-year-old female with no previous history of depression
- She is artistically gifted, the mother of two children (17-yr-old daughter, 5-yr-old son)
- Major depression began without obvious trigger about 2 years ago and her gynecologist prescribed an SSRI
- Family history: bipolar illness in paternal grandfather

File name location
3

Profile: Ashley (cont'd)

- She presents to you suffering from insomnia, irritability, distractibility, and racing thoughts. She has a tendency to be over-talkative. On probing, you find that these symptoms began before she started on the antidepressant.

- Needs mood stabilization
  - –ZYPREXA® (olanzapine) 5 mg qhs is started
  - –She shows marked improvement in 5 days
  - –ZYPREXA is eventually increased to 10 mg qhs with a good response

File name location
4

Profile: Andrea

- Andrea is a 21-yr-old Ivy league student
- During summer vacation, there is a marked change in her behavior
  - –Ordinarily quite extroverted, she becomes withdrawn and sullen
  - –Friends notify parents who bring her home
  - –At home, she is hypoverbal, blunted, isolative, and hypersomnic

File name location
5

Profile: Andrea (cont'd)

- Her parents suggest visiting family physician and Andrea agrees
- Upon visit to PCP, she is clearly depressed and anhedonic
- No significant medical or psychiatric history
- Family psychiatric history: a maternal aunt committed suicide, and maternal grandmother suffered repeated "nervous breakdowns"
- What is your diagnosis?

File name location
6

Profile: Andrea (cont'd)

- She is diagnosed with major depression and started on an antidepressant
  - –After 2 days on medication, she appears dramatically improved, more like her old self
  - –After 10 days of treatment, she becomes increasingly irritable, restless, anxious, hyperverbal, and experiences great difficulty sleeping
- What is happening here?

File name location

Profile: Andrea (cont'd)

- Diagnostic clues of bipolar disorder that went undetected:
  - Dramatic onset of depression
  - Early age of onset of illness
  - Family history of manic-depressive illness
  - About 2 years ago, she had an episode lasting one week, during which she spent $3000 on items she didn't need, slept only 1-2 hours some nights and not at all others, was distractible, and felt agitated and irritable. That episode resolved on its own and she did not seek treatment.
- Her rapid response to an antidepressant was also suggestive of bipolar illness
- After she experienced antidepressant-mobilized mania, accurate diagnosis was made

File name location
8

Profile: Andrea (cont'd)

- New treatment plan:
  - Discontinued the antidepressant
  - Patient started on ZYPREXA® (olanzapine) 10 mg qhs
- Patient significantly improved within one week

File name location
9

Profile: Cindy

- Cindy is a 23-year-old law student who presents with "chronic depression" and anxiety
- Believing her problems began in her late teens, she says she can't remember the last time she felt good
- Medical history negative, but has been prescribed several antidepressants in the past without benefit
- She reports that most of the medications did nothing at all, but two of them made her feel "jumpy, panicky and sleepless"
- Psychiatric family history: maternal grandfather was an alcoholic; her mother has been diagnosed as dysthymic and is in long-term psychotherapy with a social worker

File name location
10

Profile: Cindy (cont'd)

- At PCP visit, she complains of sadness, lack of sustained interest in anything, insomnia and several vague physical complaints
- She also reports being easily distracted at school, irritable, unable to sit still, and has racing thoughts
- She says she has been unable to complete class assignments and her grades are slipping
- What is your diagnosis?

Profile: Cindy (cont'd)

- Diagnosis of dysthymic disorder is made, and she is started on an antidepressant
- Within 4 days, she becomes very anxious, agitated and hyperactive, with pressured speech and racing thoughts
- Now, diagnosis of antidepressant exacerbation of mixed symptom state to full-blown mania is made
- Patient begins taking ZYPREXA® (olanzapine) 10 mg qhs, and within one week she reports significant improvement

Group Questions

- What are your current treatment strategies for patients similar to those described today?
- Which specific symptoms do you attempt to resolve first?
- Once those symptoms are resolved, what are your goals for that patient?
- When treating these types of patients, how do you determine which medication to use? Which is more important – the efficacy profile, or the side effect profile of the medication?
- What benefits have you seen in using ZYPREXA® (olanzapine) for these patients?

Group Questions (cont'd)

- There are at least two commonly used algorithms for dosing: One says "start low and go slow" and the other declares "the starting dose is the therapeutic dose." When considering ZYPREXA® (olanzapine), which dosing algorithm makes the most sense to you?
- On what dose would you start a patient with complicated mood symptoms? At what dose would you expect to find a therapeutic effect?

File name location
14

Group Questions (cont'd)

- The APA Guidelines and the Texas Medicaid Algorithm Project (TMAP) were published in the *American Journal of Psychiatry* and *The Journal of Clinical Psychiatry* respectively. Both algorithms recommend ZYPREXA® (olanzapine) as a first-line treatment for bipolar mania, like divalproex and lithium. This now makes ZYPREXA the only treatment recommended first line for schizophrenia AND bipolar mania by BOTH of these highly recognized panels.

- Does this impact your view of ZYPREXA as a mood stabilizer for your patients suffering from bipolar mania? Why or why not?

File name location
15

Safety Information

- ZYPREXA® (olanzapine) is indicated for the treatment of schizophrenia and for acute mania associated with bipolar I disorder.

- In 6-week acute-phase schizophrenia trials, the most common treatment-emergent adverse event associated with ZYPREXA was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, and postural hypotension.

Safety Information (cont.)

- In short-term, placebo-controlled trials in bipolar mania, the most common treatment-emergent events associated with ZYPREXA® (olanzapine) were somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

- In premarketing trials, some patients taking ZYPREXA may have experienced orthostatic hypotension associated with dizziness, tachycardia, and, in some cases, syncope (15/2500, 0.6%).

File name location
17

Safety Information (cont.)

- In placebo-controlled studies involving schizophrenia patients, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA® (olanzapine) compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

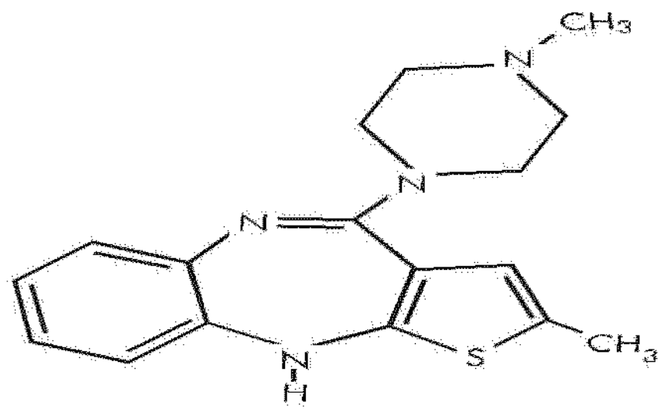
- Prescribing should be consistent with the need to minimize tardive dyskinesia, seizures, and orthostatic hypotension.

See accompanying prescribing information for ZYPREXA.

File name location
18

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

DESCRIPTION: ZYPREXA® (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5] benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



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

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), F D & 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 edible ink which contains F D & 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_i=4 and 11nM, respectively), dopamine D_{1-4} (K_i=11-31nM), muscarinic M_{1-5} (K_i=1.9-25 nM), histamine H_1 (K_i=7nM), and adrenergic α_1 receptors (K_i=19nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i > 10µM).

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 ($5HT_2$) 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 $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 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 α_1-acid glycoprotein.

Metabolism and Elimination—Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as uncharged 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 for total radioactivity, indicating significant exposure to metabolites. 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 suggest 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 to 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 needed.

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 are administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and 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. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

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 in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively 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=149) 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, respectively) were superior to placebo on BPRS 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 on 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—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 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.

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—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).

The effectiveness of ZYPREXA for longer-term use, that is, for more than 4 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.

WARNINGS: *Neuroleptic Malignant Syndrome (NMS)*—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, 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 creatinine 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 pharmacological 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 treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (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. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness 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 reassessed periodically.

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.

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 α_1-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). A more gradual titration to the target dose 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 D_2 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 if 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 release, an increase in mammary gland neoplasia was observed in the olanzapine 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 insufficient 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 patients in 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 should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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.

Two flexible-dose studies of olanzapine (started at 2.5 mg/day and titrated up to a maximum of 15 mg/day based on investigator judgment; mean modal dose 4.2 mg) and placebo were conducted in Parkinson's disease patients (mean age: 71 years, range: 50-88 years) having drug-induced (dopamine agonist) psychosis. Patients were required to be stable on the lowest dose of anti-Parkinsonian medications deemed necessary clinically to control the motor symptoms of Parkinson's disease upon entry in the studies and to remain on the same anti-Parkinsonian medications and dosages throughout the studies. The following treatment-emergent adverse events were reported in the olanzapine-treated group at an incidence of at least 5% for olanzapine and two-fold or more in excess of the placebo-treated group: worsening of Parkinsonian symptomatology, hallucinations, somnolence, increased salivation, asthenia, and peripheral edema. The rate of discontinuation in these studies due to adverse events for olanzapine was 20% vs 3% with placebo. Discontinuations due to worsening of Parkinsonian symptomatology (8% 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 and/or Parkinson's disease (*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).

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.

Phenylketonurics—ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (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—The 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.

The Effect of Other Drugs on Olanzapine—Agents that induce 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 need to be considered with specific drugs.

Charcoal—The administration of activated charcoal (1 g) reduced the C_{max} 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 16%) 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 C_{max} following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

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 vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

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 CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

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, lithium, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

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

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

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

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

Placental transfer of olanzapine occurs in rat pups.

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

Labor and Delivery—Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

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

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease and in Parkinson's disease patients with drug-induced (dopamine agonist) psychosis have suggested that there may be a different tolerability profile in these populations compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia and/or Parkinson's disease. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The information below is derived from a clinical trial database for olanzapine consisting of 4189 patients with approximately 2665 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1996; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional clinical trials as of May 1, 1997.

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

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

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

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms which were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during

treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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

Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials—The following findings are based on the short-term, placebo-controlled premarketing trials for schizophrenia and bipolar mania and a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials—*Schizophrenia*—Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for olanzapine vs 0% for placebo) (*see* PRECAUTIONS).

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

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials—The most commonly observed adverse events associated with the use of olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

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%

[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 TRIALS[1]

	Percentage of Patients Reporting Event			Percentage of Patients Reporting Event	
Body System/Adverse Event	Olanzapine (N=532)	Placebo (N=294)	Body System/Adverse Event	Olanzapine (N=532)	Placebo (N=294)
Body as a Whole			**Musculoskeletal System**		
Accidental injury	12%	8%	Extremity pain (other than joint)	5%	3%
Asthenia	10%	9%	Joint pain	5%	3%
Fever	6%	2%	**Nervous System**		
Back pain	5%	2%	Somnolence	29%	13%
Chest pain	3%	1%	Insomnia	12%	11%
Cardiovascular System			Dizziness	11%	4%
Postural hypotension	3%	1%	Abnormal gait	6%	1%
Tachycardia	3%	1%	Tremor	4%	3%
Hypertension	2%	1%	Akathisia	3%	2%
Digestive System			Hypertonia	3%	2%
Dry mouth	9%	5%	Articulation impairment	2%	1%
Constipation	9%	4%	**Respiratory System**		
Dyspepsia	7%	5%	Rhinitis	7%	6%
Vomiting	4%	3%	Cough increased	6%	3%
Increased appetite	3%	2%	Pharyngitis	4%	3%
Hemic and Lymphatic System			**Special Senses**		
Ecchymosis	5%	3%	Amblyopia	3%	2%
Metabolic and Nutritional Disorders			**Urogenital System**		
			Urinary incontinence	2%	1%
Weight gain	5%	3%	Urinary tract infection	2%	1%
Peripheral edema	3%	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, dysmenorrhea[2], hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder[3], 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.

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 PHASE*

	Percentage of Patients			
	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.

	Percentage of Patients Reporting Event			
Adverse 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%

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 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

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

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 hematologic 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.

In two clinical trials in schizophrenia patients (n=107) where random triglycerides were measured, 1.9% of olanzapine-treated patients with baseline random triglycerides below the upper limits of normal for fasting triglycerides showed a random triglyceride level greater than two-fold the upper limit of normal for fasting triglycerides, with no patients showing greater than a three-fold increase, at any point during 8 weeks of treatment. This analysis used upper limit of normal reference values for fasting triglycerides since the normal range for random triglyceride values has not been established. Given the large intrasubject variability of random triglyceride levels, the clinical significance of this finding is unclear.

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 use 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 (4189 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, thrombocythemia, and thrombocytopenia; *Rare:* normocytic anemia.

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

Musculoskefetal 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, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, 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 analytes or ECG. Vital signs were usually within normal limits following overdoses.

During the first 2 years of marketing, Eli Lilly and Company received reports of 178 cases of possible 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 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 and ventilation, 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 hypotensive 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 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). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Bipolar Mania—Usual Dose—Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 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 efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

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

Maintenance Treatment—There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with olanzapine. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of olanzapine in such longer-term treatment (i.e., beyond 3-4 weeks).

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)—After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

HOW SUPPLIED:

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and 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-0002-4117-04	NDC-0002-4415-04	NDC-0002-4420-04

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

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

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

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of R. P. Scherer Corporation.
*ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

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

Protect from light and moisture.

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

PV 3395 AMP [1101]

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