PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr**ZYPREXA®** (olanzapine) Tablets
Oral, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg

Pr**ZYPREXA® ZYDIS®** (olanzapine) Orally Disintegrating Tablets
Oral, 5 mg, 10 mg, 15 mg, 20 mg

Pr**ZYPREXA® IntraMuscular** (olanzapine tartrate for injection)
Intramuscular, 10 mg olanzapine/vial

N05AH03, Antipsychotic Agent

CHEPLAPHARM Registration GmbH
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Germany

Date of Initial Authorization:
Zyprexa 7.5 mg tablets: Oct. 30, 1996

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RECENT MAJOR LABEL CHANGES

N/A	

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZYPREXA (oral olanzapine) is indicated for

- the acute treatment of schizophrenia and related psychotic disorders
- maintenance treatment of schizophrenia and related psychotic disorders.

In controlled clinical trials, ZYPREXA was found to improve both positive and negative symptoms.

ZYPREXA has been shown to be effective in maintaining clinical improvement during 1-year of continuation therapy in patients who had shown an initial treatment response.

ZYPREXA (oral olanzapine) is indicated for the acute treatment of

- manic or mixed episodes in bipolar I disorder.

Olanzapine may be used as monotherapy or cotherapy with agents commonly used in the treatment of acute bipolar disorder (e.g., lithium or divalproex sodium).

The efficacy of ZYPREXA as monotherapy maintenance treatment in bipolar patients with manic or mixed episodes who responded to acute treatment with ZYPREXA was demonstrated in two 1-year "time to relapse" trials (see 14 CLINICAL TRIALS).

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 4 DOSAGE AND ADMINISTRATION section).

ZYPREXA IntraMuscular (intramuscular olanzapine) is indicated for

- the rapid control of agitation in patients with schizophrenia and
- related psychotic disorders, and
- bipolar mania.

The efficacy of ZYPREXA IntraMuscular for the control of agitation was established in 2 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia and one short-term (24 hours) placebo-controlled trial in agitated patients with mania associated with bipolar disorder (see 14 CLINICAL TRIALS section).

1.1 Pediatrics

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Zyprexa in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 1.7.1.3 Pediatrics

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population with dementia is associated with differences in safety or effectiveness. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 1.7.1.4 Geriatrics).

2. CONTRAINDICATIONS

ZYPREXA (olanzapine) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the

formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia:
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. (See 7 WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General Considerations for Oral Dosing in Special Populations
Elderly or Debilitated Patients:
In clinical trials, 44 patients with schizophrenia or related disorders who were 65 years of age or over were treated with ZYPREXA (5-20 mg daily) (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations). Given the limited experience with ZYPREXA in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, ZYPREXA should be used with caution.

The recommended starting dose is 5 mg in patients who are elderly, debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of ZYPREXA (e.g., nonsmoking female patients), or who may be pharmacodynamically more sensitive to ZYPREXA. When indicated, dose escalation should be performed with caution in these patients.

Patients with Hepatic and/or Renal Impairment:
As clinical experience is lacking in these patients, the lower initial starting dose and slower titration to initial target dose should be considered. Further dose escalation, when indicated, should be conservative (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

General Considerations for Intramuscular Dosing in Special Populations
Elderly or Debilitated Patients:
Lower doses (e.g., 2.5 mg) should be considered when clinical factors warrant.

4.2 Recommended Dose and Dosage Adjustment

ORAL ADMINISTRATION

Bioequivalence of the 15 mg and 20 mg tablets to multiple 5 mg tablets has been demonstrated. These tablet formulations are equally well absorbed and can be readily interchanged. Pharmacokinetic studies showed that the ZYPREXA Tablets and ZYPREXA ZYDIS dosage forms are bioequivalent. ZYPREXA ZYDIS orally disintegrating tablets can be used as an alternative to ZYPREXA Tablets. (see 14.2 Study results).

Schizophrenia and Related Disorders

Adults: ZYPREXA (olanzapine) should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg, 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 ZYPREXA would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/ decrements of 5 mg per day are recommended. An increase to a dose greater than target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is normally recommended only after clinical assessment.

In clinical trials a dose range of 5-20 mg/day was studied (see 14 CLINICAL TRIALS).

Doses above 20 mg/day have been evaluated from a safety perspective (see Table 6 in Adverse Events, Dose-Dependent Adverse Events subsection); however, efficacy at doses above 20 mg/day has not been systematically evaluated.

Maintenance Therapy in Schizophrenia:

It is recommended that responding patients with schizophrenia be continued on ZYPREXA at the lowest dose needed to maintain remission. Patients should be reassessed periodically to determine the need for maintenance treatment. While there is no body of evidence available to answer the question of how long the patient should be treated with ZYPREXA, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs.

Bipolar Disorder

Bipolar Mania

Adults: The recommended starting dose for olanzapine is 15 mg administered once a day in monotherapy and 10 mg daily in combination therapy.

It may be given without regard to meals as its absorption is not affected by food. The dosage range of olanzapine is from 5 mg to 20 mg per day. Daily dosage should be adjusted in response to clinical assessment.

Maintenance Therapy in Bipolar Disorder:

Patients who have been receiving and responding to ZYPREXA for the treatment of acute manic or mixed episodes of bipolar disorder should initially continue maintenance therapy at the same dose (see 14 CLINICAL TRIALS). Subsequent daily dosage should be adjusted on the basis of clinical status within a range of 5-20 mg per day.

Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Health Canada has not authorized an indication for pediatric use.

INTRAMUSCULAR ADMINISTRATION

In clinical trials, individual doses of 5 mg, 7.5 mg and 10 mg of intramuscular olanzapine for injection have been shown to be effective in controlling agitation in patients with schizophrenia (see 14 CLINICAL TRIALS). Individual doses of more than 10 mg of intramuscular olanzapine have not been studied and are not recommended.

Usual Dose for Agitated Patients with Schizophrenia and Bipolar Mania:

The usual initial dose for olanzapine injection is 10 mg, administered as a single intramuscular injection. A lower dose (5 mg or 7.5 mg) may be given, on the basis of individual clinical status.

Repeat and Maximum Dose:

In clinical trials over a 24 hour period, a minority of patients required a second dose, and only a small percent of patients required a third dose of ZYPREXA IntraMuscular (see 14 CLINICAL TRIALS). Thus safety information on the use of repeated doses of ZYPREXA IntraMuscular is limited. Nevertheless, if warranted by the clinical situation, a second dose, 5-10 mg, may be administered 2 hours after the first injection. A third dose, if required, should be

given no sooner than four hours after the second dose. The safety of total daily doses greater than 30 mg has not been evaluated in clinical trials.

The recommended maximum daily dose of olanzapine (oral and IM) is 20 mg, with no more than three injections in a 24 hour period.

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

Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended (see 7 WARNINGS AND PRECAUTIONS).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

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

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
5 mL	2.1 mL of Sterile Water for Injection	2 mL	5 mg/mL

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

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

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

Ongoing Therapy:
If ongoing olanzapine therapy is clinically indicated, treatment with intramuscular olanzapine for injection should be discontinued and oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (see 4 DOSAGE AND ADMINISTRATION, Oral Administration subsection).

Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature 20°C-25°C [See USP] for up to 1 hour if necessary. **Discard any unused portion of reconstituted ZYPREXA IntraMuscular** (see 11 STORAGE AND STABILITY)

4.4 Administration

ZYPREXA ZYDIS orally disintegrating tablet is intended for oral administration only. It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid.

The orally disintegrating tablet breaks easily and should be handled carefully, with dry hands. Direct contact with hands should be avoided if possible. One blister cell must be separated from the strip prior to peeling the blister backing. The blister backing should be carefully peeled back and the orally disintegrating tablet pushed out and placed directly in the mouth. The orally disintegrating tablet may also be stirred into 125 mL (4 ounces) of water, milk, coffee, orange juice or apple juice and the contents promptly consumed.

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

Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended (see 7 WARNINGS and PRECAUTIONS).

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

4.5 Missed Dose

If a patient misses a dose by a few hours, advise patient to take as soon as he/she remembers. If most of the day has passed, advise patient to wait until the next scheduled dose. Advise patients to not take 2 doses of ZYPREXA at once.

5. OVERDOSE

Signs and Symptoms
Very common symptoms reported in olanzapine overdose (≥ 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of olanzapine overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg of oral olanzapine but survival has also been reported following acute overdose of approximately 2,000 mg of oral olanzapine.

Management of Overdose
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e., gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension.

For management of a suspected drug overdose, contact your regional Poison Control Centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Product	Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Zyprexa	oral	tablet / 2.5 mg (8 µmol)[1], 5 mg (16 µmol)[1], 7.5 mg (24 µmol)[1] , 10 mg (32 µmol)[1], 15 mg (48 µmol)[1] , 20 mg (64 µmol)[1]	*Tablets:* carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, and microcrystalline cellulose *Colour coating and ink contain some or all of the following ingredients:* FD&C Blue No.2 Aluminum Lake (15.0 mg tablets only[2]), polyethylene glycol (2.5 mg, 5.0 mg, 7.5 mg, 10.0 mg, and 20 mg tablets only), polysorbate 80 (2.5 mg, 5.0 mg, 7.5 mg, and 10.0 mg, only), Synthetic Red Iron Oxide (20.0 mg tablets only), titanium dioxide, triacetin (15.0 mg tablets only).
Zyprexa ZYDIS	oral	orally disintegrating tablets / 5 mg (16 µmol)[1], 10 mg (32 µmol)[1], 15 mg (48 µmol)[1], 20 mg (64 µmol)[1]	aspartame, gelatin, mannitol, sodium methyl paraben and sodium propyl paraben
Zyprexa IntraMuscular	intramuscular injection	parenteral / 10 mg per vial[3]	Lactose, tartaric acid (hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH)

[1] equivalent activity of olanzapine
[2] 2.5 mg, 5.0 mg, 7.5 mg, and 10.0 mg tablets are imprinted with edible ink which contains FD&C Blue No.2 Aluminum Lake
[3] each vial contains olanzapine, as the tartrate, equivalent to 10 mg olanzapine with inactive ingredients

AVAILABILITY OF DOSAGE FORMS:
ZYPREXA Tablets:
The 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, film-coated, and imprinted in blue ink with "LILLY" and the tablet identification code. The 15 mg and 20 mg tablets are elliptical, film-coated light blue and pink, respectively, and debossed with "LILLY" and the tablet identification code.

The 2.5 mg, 5 mg, and 10 mg tablets are available in amber HDPE bottles of 7, 60, 100, 250, and 1000 tablets and in blisters. The 7.5 mg tablets are available in amber HDPE bottles of 60, 100, 250, and 1000 tablets and blisters. The 15 mg and 20 mg tablets are available in amber HDPE bottles of 7, 30, 100, and 1000 tablets and in blisters.

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Imprinted or Debossed	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420

ZYPREXA ZYDIS Orally Disintegrating Tablets:
The 5 mg, 10 mg, 15 mg, and 20 mg tablets are yellow and round. The tablets are supplied in aluminum blister strips in cartons of 7 tablets or 28 tablets per carton.

ZYPREXA IntraMuscular:
ZYPREXA IntraMuscular is available as single use 5 mL vials in packages of 1s (VL7597).

For reconstitution information, please see 4.3 DOSAGE AND ADMINISTRATION - Reconstitution.

ZYPREXA IntraMuscular is intended for intramuscular use only.

Phenylketonurics: ZYPREXA ZYDIS contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg oral lyophilisate, respectively).

7. WARNINGS AND PRECAUTIONS

Please see **3** SERIOUS WARNINGS AND PRECAUTIONS BOX

General

Clinical experience with olanzapine in patients with concomitant illness is limited. Caution is thus advised when using ZYPREXA in patients with diseases or conditions that could affect the metabolism or the pharmacodynamic activity of olanzapine (see 4 DOSAGE AND ADMINISTRATION section and 10 CLINICAL PHARMACOLOGY).

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 ZYPREXA for patients who will be experiencing conditions which may contribute to an elevation of core temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Falls:
ZYPREXA may cause somnolence, postural (orthostatic) hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Anticholinergic effects
As ZYPREXA demonstrated anticholinergic activity *in vitro*, caution is advised when prescribing for patients with symptomatic prostatic enlargement, narrow-angle glaucoma or paralytic ileus and related conditions.

Carcinogenesis and Mutagenesis
For animal data, see 16 NON-CLINICAL TOXICOLOGY section.

Cardiovascular

ZYPREXA has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these conditions were excluded from pre-marketing clinical trials. Due to the more rapid and higher peak plasma concentrations following intramuscular compared to oral administration (see 10 CLINICAL PHARMACOLOGY section), particular caution is advised with the use of ZYPREXA IntraMuscular. ZYPREXA IntraMuscular should not be administered to patients with unstable medical conditions, such as acute or unstable cardiovascular conditions such as myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, or sick sinus syndrome. If the patient's medical history with regard to unstable medical conditions cannot be determined, the risks and benefits of IM olanzapine should be considered in relation to other alternative treatments.

Hypotension and Syncope:

As with other drugs that have high alpha-1 adrenergic receptor blocking activity, ZYPREXA may induce orthostatic hypotension, tachycardia, dizziness, and sometimes syncope, especially at the initiation of treatment. In a clinical trial database of 2500 patients treated with oral ZYPREXA, syncope was reported in 0.6% (15/2500). The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (see 4 DOSAGE AND ADMINISTRATION section). A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension and/or syncope associated with bradycardia has been observed infrequently with ZYPREXA IntraMuscular.

Patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 2 to 4 hours following injection. Patients should remain recumbent if dizzy or drowsy after injection until examination indicates that they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation.

Caution is necessary in patients who receive intramuscular olanzapine with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine and/or other drugs with CNS depressant activity has been associated with post-marketing reports of serious adverse events, including fatalities and is therefore not recommended. If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. If the patient has received parenteral benzodiazepine, IM olanzapine administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression (see 9 DRUG INTERACTIONS section).

ZYPREXA 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).

QT Interval:

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF < 500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see 8 ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Cardiac Death:

In a retrospective observational study, patients treated with atypical antipsychotics (including olanzapine) or typical antipsychotics had a similar dose-related increase of presumed sudden cardiac death (SCD) compared to

non-users of antipsychotics (almost twice the risk than that for non-users). In postmarketing reports with olanzapine, the event of SCD has been reported very rarely.

Driving and Operating Machinery

Potential Effect on Cognitive and Motor Performance:
Because ZYPREXA may cause somnolence, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that ZYPREXA therapy does not affect them adversely.

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism
Weight Gain:
Olanzapine was associated with weight gain during clinical trials. Clinically significant weight gain was observed across all baseline body mass index (BMI) categories (see 8 ADVERSE REACTIONS, Other Adverse Events Observed During Clinical Trials with Oral and Intramuscular Olanzapine Across All Indications, Weight Changes). Using pooled data from patients treated with olanzapine over the dosage range of 5 mg to 20 mg per day mean gain was 5.4 kg. The mean change in weight was comparable for patients with schizophrenia and bipolar mania. A retrospective analysis of 573 patients receiving olanzapine for up to 3 years found that dose was not a significant predictor of greater long-term changes in weight.

In long-term studies (at least 48 weeks), both the magnitude of weight gain and the proportion of olanzapine-treated patients who had clinically significant weight gain were greater than in short-term studies. The percentage of patients who gained ≥ 25% of their baseline body weight with long-term exposure was very common (≥ 10%).

Hyperglycaemia:
As with some other antipsychotics, exacerbation of pre-existing diabetes and hyperglycaemia have been reported rarely and diabetic ketoacidosis and diabetic coma including some fatal cases have been reported very rarely during the use of ZYPREXA, sometimes in patients with no reported history of hyperglycaemia (see 8 ADVERSE REACTIONS; Post-Market Adverse Drug Reactions section). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Patients should have baseline and periodic monitoring of blood glucose and body weight.

In clinical trials (up to 52 weeks) olanzapine was associated with a greater mean change in glucose relative to placebo. Treatment-emergent clinically significant changes in fasting glucose were observed in patients with or without evidence of glucose dysregulation at baseline (see 8 ADVERSE REACTIONS, Other Adverse Events Observed During Clinical Trials with Oral and Intramuscular Olanzapine Across All Indications, Glucose Changes).

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

Hyperprolactinemia:
As with other drugs that block dopamine D_2 and/or serotonin 5-HT_2 receptors, olanzapine may elevate prolactin levels. Elevations associated with ZYPREXA treatment are generally mild, and may decline during continued administration.

Since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, ZYPREXA should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering ZYPREXA treatment in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea, and menorrhagia.

As is common with compounds which stimulate prolactin release, the administration of olanzapine resulted in an increase in the incidence of mammary neoplasms in both rats and mice. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Lipids:
Increases in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. Treatment-emergent clinically significant changes in fasting lipids were observed in patients with or without evidence of dyslipidemia at baseline (see 8 ADVERSE REACTIONS; Other Adverse Events Observed During Clinical Trials with Oral and Intramuscular Olanzapine Across All Indications, Lipids subsection). Appropriate clinical monitoring is recommended, including baseline and follow-up lipid evaluations.

Gastrointestinal
Antiemetic Effect:
Consistent with its dopamine antagonist effects, olanzapine may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumour or intestinal obstruction.

Genitourinary
Priapism:
Rare cases of priapism have been reported with antipsychotic use, such as ZYPREXA. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment. The most likely mechanism of action of priapism is a relative decrease in sympathetic tone.

Urinary Retention:
ZYPREXA possesses anticholinergic properties, which can lead to adverse drug reactions such as urinary retention. There have been several serious post-marketing reports of urinary retention in ZYPREXA-treated patients and in some cases, catheterization was required. ZYPREXA should be prescribed with caution in patients with a current diagnosis or prior history of urinary retention and in patients with other risk factors for urinary retention (e.g. benign prostatic hyperplasia). ZYPREXA should also be prescribed with caution in patients receiving medications with anticholinergic activity that can affect voiding.

Hematologic
Venous Thromboembolism:
Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported in temporal association with antipsychotic drugs, including ZYPREXA, in case reports and/or observational studies. When prescribing ZYPREXA, all potential risk factors for VTE should be identified and preventative measures undertaken, particularly since patients with schizophrenia often present with risk factors for VTE. Very rare cases of VTE have been reported in ZYPREXA-treated patients during the post-marketing period.

Hematologic Indices:
In oral olanzapine clinical trials, there were no data to suggest ZYPREXA adversely affected bone marrow function, even in patients with a history of clozapine-associated neutropenia or leukopenia. ZYPREXA was associated with a 5.7% incidence of mainly transient treatment-emergent elevations of eosinophil counts above the normal range. Elevations were not associated with any symptoms, identifiable allergic phenomena, or changes in other hematologic indices. Rare cases of leukopenia have been reported with ZYPREXA. In case of symptoms of infection, WBC count and differential count should be considered.

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting ZYPREXA and then periodically throughout treatment.

Hepatic
Small single-dose clinical pharmacology studies (see 10 CLINICAL PHARMACOLOGY section) did not reveal any major alterations in olanzapine pharmacokinetics in subjects with hepatic impairment. Given the limited clinical experience with ZYPREXA in patients with these conditions, caution should be exercised (see 4 DOSAGE AND ADMINISTRATION section).

Aminotransferase Elevations:
During pre-marketing clinical trials, therapy with oral ZYPREXA was associated with elevation of hepatic aminotransferases, primarily ALT (SGPT). Within a clinical trial database of 2280 ZYPREXA-treated patients, with baseline ALT (SGPT) levels ≤ 60 IU/L, 5.9% (134/2280) had treatment-emergent ALT (SGPT) elevations to > 120 IU/L, 1.9% (44/2280) had elevations to > 200 IU/L, and 0.2% (5/2280) had elevations to > 400 IU/L. No patients had values in excess of 700 IU/L. None of the ZYPREXA-treated patients who had elevated aminotransferase values manifested clinical symptomatology associated with liver impairment. The majority of aminotransferase elevations were seen during the first six weeks of treatment. Most elevations were transient (66%) while patients continued on ZYPREXA therapy, or falling (11%) at the last available measurement. Of the 134 ZYPREXA-treated patients whose enzyme levels increased to > 120 IU/L, 20 discontinued treatment (6 for hepatic, 14 for other reasons) while their ALT (SGPT) values were still rising. In 38 ZYPREXA-treated patients with baseline ALT (SGPT) > 90 IU/L, none experienced an elevation to > 400 IU/L.

Rare post-marketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the post-marketing period. Hepatic failure, including fatalities has also been reported very rarely in the post-marketing period. See 8.5 Post-Market Adverse Reactions section.

Precaution should be exercised when using ZYPREXA in patients with pre-existing hepatic disorders, in patients who are being treated with potentially hepatotoxic drugs, or if treatment-emergent signs or symptoms of hepatic impairment appear.

For patients who have known or suspected abnormal hepatic function prior to starting ZYPREXA, standard clinical assessment including measurement of aminotransferase levels is recommended. Periodic clinical reassessment with aminotransferase levels is recommended for such patients, as well as for patients who develop any signs and symptoms suggestive of a new onset liver disorder during ZYPREXA therapy.

Neurologic
Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including ZYPREXA.

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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify 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 all antipsychotic drugs including ZYPREXA and other drugs not essential to 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 for uncomplicated NMS.

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

Tardive Dyskinesia:
Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible involuntary dyskinetic movements, is associated with the use of antipsychotic drugs. Tardive dyskinesia occurs more frequently in elderly patients; however, patients of any age can be affected. It is unknown whether antipsychotic drugs may differ in their potential to cause TD. However, during long-term, double-blind, extension schizophrenia maintenance trials (894 olanzapine-treated patients; median olanzapine treatment, 237 days), ZYPREXA was associated with a statistically significantly lower incidence of treatment-emergent dyskinesia compared to haloperidol. During long-term, double-blind, monotherapy extension bipolar maintenance trials (567 olanzapine-treated patients, for up to 1 year), there were no cases of TD in the ZYPREXA arms, as determined by either reported adverse events or the Abnormal Involuntary Movement Scale (AIMS). TD has been reported very rarely (≤ 0.0025%) in post-market surveillance.

The risk of developing tardive dyskinesia and the chance of it becoming irreversible are believed to increase as the duration of treatment and the cumulative dose of antipsychotic drug increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment itself, however, may suppress the signs and symptoms of tardive dyskinesia, thereby masking the underlying process.

Given these considerations, ZYPREXA should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. As with any antipsychotic drug, ZYPREXA should be reserved for patients who appear to be receiving substantial benefit from the drug. In such patients the lowest effective dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs or symptoms of tardive dyskinesia appear in a patient on ZYPREXA, drug discontinuation should be considered. However, some patients may benefit from continued treatment with ZYPREXA despite the presence of the syndrome.

In clinical trials, a single case of pre-existing intracranial hypertension was exacerbated.

Seizures:
Conventional neuroleptics are known to lower seizure threshold. In clinical trials, seizures have occurred in a small number (0.9%, 22/2500) of ZYPREXA-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. ZYPREXA should be used cautiously in patients who have a history of seizures or have conditions associated with seizures or have a lowered seizure threshold.

Psychiatric

Suicide:

The possibility of suicide or attempted suicide is inherent in psychosis, and thus close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal

Small single-dose clinical pharmacology studies (see 10 CLINICAL PHARMACOLOGY section) did not reveal any major alterations in olanzapine pharmacokinetics in subjects with renal impairment. Given the limited clinical experience with ZYPREXA in patients with these conditions, caution should be exercised (see 4 DOSAGE AND ADMINISTRATION section).

Uric Acid:

In the pre-marketing clinical trial database, oral ZYPREXA was associated with mild elevations of uric acid in some patients. However, only one ZYPREXA-treated patient experienced treatment-emergent gout, and the baseline uric acid concentration for this patient was at least as large as all concentrations observed while the patient was receiving ZYPREXA.

Skin

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Severe cutaneous adverse reactions are sometimes fatal. Discontinue olanzapine if DRESS is suspected.

7.1 Special Populations

7.1.1. Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with ZYPREXA. Because human experience in pregnant females is limited, this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects:

Neonates exposed to antipsychotic drugs (including ZYPREXA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

ZYPREXA should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Labour and Delivery:

Parturition in rats was not affected by olanzapine. The effect of ZYPREXA on labour and delivery in humans is not known.

Reproductive and Developmental toxicology in animal models

Fertility studies in male and female rats and teratology studies in rats and rabbits have been conducted by the oral route. Mating performance was affected by administration of very high olanzapine doses due to sedation in male rats, but the effect was quickly reversed when treatment stopped. Estrous cycles were affected and reproduction parameters were influenced in rats given high doses. No adverse effects were observed on numbers of corpora lutea, implantations, fetal viability, or fetal weight, and there were no effects on litter size or on the survival,

growth, or development of the offspring from parents given up to 18 times the maximum daily human dose (5 mg/kg/day in rats). Although the reproductive process in female rats from mating through fertilization was not adversely affected by treatment, this evidence does not exclude a possible interference with maintenance of pregnancy at high doses of olanzapine. The reproduction studies conducted did not reveal evidence of harm to the fetus. Maternal toxicity, developmental toxicity (indicated by fetal growth retardation and slightly delayed ossification at birth), and increased numbers of nonviable offspring occurred at higher doses. However, fetal malformations were not increased. Transient modest decreases in activity levels of the progeny from females given 0.25 mg/kg/day and skeletal changes indicative of growth retardation in fetuses from females given 5 mg/kg/day were observed. Transient decreases in offspring activity have occurred at all doses; however, there were no effects on body weight, growth, mating, fertility, or live births in second-generation animals. Placental transfer of olanzapine occurs in rat fetuses (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2. Breast-feeding

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast feed an infant if they are taking ZYPREXA.

Data from animal model
Olanzapine was also detected in the milk of rats at concentrations up to three-fold higher than those in the plasma (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of ZYPREXA in children under the age of 18 years have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any changes during treatment with atypical antipsychotics, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status have been associated with adverse cardiovascular outcomes in adulthood. Weight gain and changes in other metabolic parameters associated with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

The long-term safety of atypical antipsychotics, including potential cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

A greater magnitude of weight gain and lipid alterations has been reported in adolescents compared with adults. Adolescents treated with olanzapine experienced a significantly higher incidence of elevated prolactin levels and significantly higher mean increases in prolactin levels compared with adults. Hepatic aminotransferase elevations are more common in adolescents as compared to adults. Sedation-related events are more common in adolescents as compared to adults.

See also 8 ADVERSE REACTIONS /Other Investigational Trials/Adverse Events in Adolescent Patients (ages 13-17 years).

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): The number of patients 65 years of age or over with schizophrenia or related disorders exposed to oral ZYPREXA during clinical trials was limited (N = 44). Caution should thus be exercised with the use of ZYPREXA in the elderly patient, recognizing the more frequent hepatic, renal, central nervous system,

and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population (see 4 DOSAGE AND ADMINISTRATION section).

Use in Geriatric Patients with Dementia

Overall Mortality:

Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In five placebo-controlled trials with oral ZYPREXA in this population, the incidence of mortality was 3.5% for ZYPREXA-treated patients compared to 1.5% for placebo-treated patients. ZYPREXA is not indicated in elderly patients with dementia (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Dysphagia:

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. 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.

Cerebrovascular Adverse Events (CVAEs), Including Stroke, in Elderly Patients with Dementia:

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled studies, there was a higher incidence of CVAEs in patients treated with ZYPREXA compared to patients treated with placebo (1.3% vs. 0.4%, respectively; see 8 ADVERSE REACTIONS section). ZYPREXA is not approved for the treatment of elderly patients with dementia.

There is insufficient evidence to determine whether CVAEs in elderly patients with dementia are associated specifically with ZYPREXA or all antipsychotic agents. Clinical trial data appear to suggest that patients with a dementia diagnosis of vascular or mixed type had a higher likelihood of experiencing CVAEs than other types of dementia.

The risks and benefits of the use of ZYPREXA in elderly patients with dementia should be assessed taking into account the risk predictors for CVAEs in the individual patient. Patients/caregivers should be advised to immediately report signs and symptoms of potential CVAEs, such as sudden weakness or numbness in the face, arms, or legs, and speech or vision problems.

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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. It is important to emphasize that although the events were reported during therapy, they were not necessarily caused by the therapy.

ORAL ADMINISTRATION:

The most commonly reported adverse reactions in patients with schizophrenia that were reported more frequently with Zyprexa oral therapy than with placebo were discontinuation due to ALT (SGPT) elevation, dizziness, constipation, personality disorder, weight gain, akathisia, and postural hypotension (see 7 WARNINGS AND PRECAUTIONS).

The most commonly reported adverse reactions in patients with bipolar disorder that were reported more frequently with Zyprexa oral therapy than with placebo were somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, weight gain, back pain, speech disorder, increased salivation, amnesia, paresthesia, and tremor (see 7 WARNINGS AND PRECAUTIONS).

INTRAMUSCULAR ADMINISTRATION:
The only adverse event observed at a higher incidence following intramuscular administration of Zyprexa in comparison to Placebo in agitated patients with schizophrenia or bipolar mania was somnolence (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

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 figures cited, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the populations studied. Information in tabular format can be found in Table 2 and Table 3. The information included in these tables is also outlined in the following text sections. Adverse events associated with discontinuation are considered separately.

Incidence of Adverse Events Associated with Discontinuation:
ORAL ADMINISTRATION
Schizophrenia and Related Disorders:
In short-term, placebo-controlled trials, there was no statistically significant difference in rates of discontinuation of ZYPREXA or placebo attributed to adverse events. Overall, 5% of ZYPREXA-treated patients discontinued treatment for adverse events compared with 6% of placebo-treated patients. Discontinuations due to ALT (SGPT) elevations, however, were considered to be drug related (2% for olanzapine versus 0% for placebo) (see 7 WARNINGS AND PRECAUTIONS, Renal subsection).

Bipolar Disorder:
Bipolar Mania
In short-term, placebo-controlled clinical trials, there was no difference overall in the incidence of discontinuation due to adverse events (2% for olanzapine versus 2% for placebo).

Bipolar Maintenance
In the long-term (1-year), placebo-controlled clinical trial, of the 225 ZYPREXA-treated patients, 16% (n = 35) discontinued due to an adverse event, compared with 9% (n = 12) of 136 placebo-treated patients.

In the long-term (1-year), active-controlled clinical trial, of the 217 ZYPREXA-treated patients, 19% (n = 41) discontinued due to an adverse event, compared with 26% (n = 55) of 214 lithium-treated patients.

All Short-Term Trials - Schizophrenia and Bipolar Mania Trials:
In short-term, active-controlled clinical trials, of the 1796 oral ZYPREXA-treated patients in comparative clinical trials with haloperidol, 98 (5%) discontinued treatment for adverse events compared with 66 of 810 (8%) haloperidol-treated patients.

All Short-Term Trials - Overall Integrated Safety Database:
In a pre-marketing clinical trial database of 2500 ZYPREXA-treated patients, 14.9% (372/2500) discontinued due to an adverse event. About half (183/372) of these discontinuations were associated with the underlying psychopathology. Other adverse events most commonly (incidence of 0.5% - 0.6%) reported as the reason for discontinuation among olanzapine-treated patients were: ALT (SGPT) increased, unintended pregnancy, creatine phosphokinase increased, and convulsion.

INTRAMUSCULAR ADMINISTRATION
In short-term, placebo-controlled trials, there was little difference overall in the incidence of discontinuation due to adverse events (0.4%) for intramuscular olanzapine for injection vs. placebo (0%).

In short-term, active-controlled clinical trials, there was little difference overall in the incidence of discontinuations due to adverse events for patients treated with intramuscular olanzapine (0.6%) vs. intramuscular haloperidol-treated groups (1.8%).

In the overall integrated safety database, of the 722 patients treated with intramuscular olanzapine, a total of 5 (0.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anxiety, maculopapular rash, agitation, hostility and tachycardia.

Incidence of Commonly Observed Adverse Events:
ORAL ADMINISTRATION

Schizophrenia and Related Disorders:
In the schizophrenia placebo-controlled trials, the most commonly observed adverse events associated with the use of olanzapine (incidence of ≥ 5% and at least twice placebo) were: dizziness (11% for olanzapine vs 4% for placebo), constipation (9% vs 3%), ALT (SGPT) increased (8% vs 3%), personality disorder (8% vs 4%), weight gain (6% vs 1%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

Bipolar Disorder:
Bipolar Mania
In the bipolar mania monotherapy placebo-controlled trials, the most commonly observed adverse events associated with the use of olanzapine (incidence of ≥ 5% and at least twice placebo) were: somnolence (35% vs 13%), dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).

In 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: dry mouth (32% for olanzapine combination vs 9% for placebo), weight gain (26% vs 7%), increased appetite (24% vs 8%), dizziness (14% vs 7%), back pain (8% vs 4%), constipation (8% vs 4%), speech disorder (7% vs 1%), increased salivation (6% vs 2%), amnesia (5% vs 2%), and paresthesia (5% vs 2%). In addition to the latter list of adverse events identified during bipolar mania combination clinical trials tremor (≥ 10%) has also been identified.

Bipolar Maintenance
In the one-year 'time to relapse' placebo-controlled clinical trial in bipolar disorder, the most commonly observed adverse events associated with olanzapine (incidence of ≥ 5% and at least twice placebo) were: weight increased (8% for olanzapine vs 1.5% for placebo), headache NOS (6.7% vs 2.9%), fatigue (6.2% vs 1.5%), depression (5.8% vs 2.9%).

Other Indication Trials:
Abnormal gait and falls have been observed very commonly (≥ 10%) in clinical trials with elderly patients with dementia-related psychosis. Also, urinary incontinence and pneumonia were commonly reported (≥ 1% and < 10%) in these patients.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

INTRAMUSCULAR ADMINISTRATION
There was one adverse event (somnolence) observed at an incidence of 5-6% or greater among intramuscular olanzapine 10 mg for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled pre-marketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

Intramuscular olanzapine for injection was commonly associated (< 10% and ≥ 1%) with bradycardia, hypotension, and tachycardia in clinical trials (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular subsection).

Adverse Events Occurring at an Incidence of 1% or More Among Oral Olanzapine-Treated Patients:

Certain portions of the discussion below relating to objective or numeric safety parameters are derived from studies in patients with schizophrenia and have not been duplicated for bipolar disorder trials. However, this information is also generally applicable to bipolar disorder. Table 2 enumerates the incidence of treatment-emergent adverse events, rounded to the nearest percent, that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with oral ZYPREXA (doses ≥ 2.5 mg/day) where the incidence in patients treated with ZYPREXA was greater than the incidence in placebo-treated patients.

Table 2: Schizophrenia Trials: Treatment-Emergent Adverse Events Incidence in Placebo-Controlled Clinical Trials with Oral Olanzapine - Acute Phase[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**ZYPREXA (N = 248)**	**Placebo (N = 118)**
Body As a Whole		
Headache	17%	15%
Pain	10%	9%
Fever	5%	3%
Abdominal pain	4%	2%
Back pain	4%	3%
Chest pain	4%	2%
Neck rigidity	2%	1%
Intentional injury	1%	0%
Cardiovascular System		
Postural hypotension	5%	2%
Tachycardia	4%	1%
Hypotension	2%	1%
Digestive System		
Constipation	9%	3%
Dry mouth	7%	4%
Gamma glutamyl transpeptidase increased	2%	1%
Increased appetite	2%	1%
Hemic and Lymphatic		
Leukopenia	1%	0%
Metabolic and Nutritional Disorders		
SGPT increased	8%	3%
Weight gain[2]	6%	1%
Edema	2%	0%
Peripheral edema	2%	0%
SGOT increased	2%	0%
Creatine phosphokinase increased	1%	0%
Musculoskeletal System		
Arthralgia	3%	2%
Joint disorder	2%	1%
Twitching	2%	1%
Nervous System		

Body System/Adverse Event	Percentage of Patients Reporting Event	
	ZYPREXA (N = 248)	Placebo (N = 118)
Somnolence[2]	26%	15%
Agitation	23%	17%
Insomnia	20%	19%
Nervousness	16%	14%
Hostility	15%	14%
Dizziness[2]	11%	4%
Anxiety	9%	8%
Personality disorder	8%	4%
Akathisia[2]	5%	1%
Hypertonia	4%	3%
Speech disorder	4%	1%
Tremor	4%	3%
Amnesia	2%	0%
Drug dependence	2%	0%
Euphoria	2%	0%
Neurosis	1%	0%
Respiratory System		
Rhinitis	10%	6%
Cough increased	5%	3%
Pharyngitis	5%	3%
Skin and Appendages		
Fungal dermatitis	2%	0%
Vesiculobullous rash	2%	1%
Special Senses		
Amblyopia	5%	4%
Blepharitis	2%	1%
Eye disorder	2%	1%
Corneal lesion	1%	0%
Urogenital System		
Menstrual disorder[3]	2%	0%

[1] The following events had an incidence equal to or less than placebo: abnormal dreams, accidental injury, anorexia, apathy, asthenia, cogwheel rigidity, confusion, conjunctivitis, depression, diarrhea, dysmenorrhea[3], dyspepsia, ecchymosis, emotional lability, hallucinations, hyperkinesia, hypertension, hypokinesia, libido increased, myalgia, nausea, paranoid reaction, paresthesia, pruritus, rash, schizophrenic reaction, sweating, thinking abnormal, tooth caries, vaginitis[3], vomiting.

[2] Statistically significantly more frequent in patients treated with oral ZYPREXA than in patients treated with placebo.

[3] Denominator used was for females only (N = 41 ZYPREXA; N = 23 Placebo).

Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular Olanzapine for Injection-Treated Patients:

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 1% or more of patients treated with intramuscular olanzapine for injection and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania.

Table 3: Treatment-Emergent Adverse Events: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar Mania[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N = 415)**	**Placebo (N = 150)**
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Dizziness	4	2
Somnolence	6	3
Tremor	1	0

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

Weight Changes:
During acute therapy (up to 6 weeks) in controlled clinical trials comparing ZYPREXA with placebo in the treatment of schizophrenia, the percentages of patients with weight gain ≥ 7% of baseline body weight at any time were 29% for ZYPREXA and 3% for placebo, which was a statistically significant difference. The average weight gain during acute therapy in patients treated with ZYPREXA was 2.8 kg. Clinically significant weight gain was observed across all baseline body mass index (BMI) categories. In long-term extension schizophrenia trials, there was an average gain of 5.4 kg, and 56% of olanzapine-treated patients with weight gain > 7% of baseline body weight. In long-term extension bipolar maintenance trials, there was a mean weight gain of 3.8 kg, and with 31% of olanzapine-treated patients with weight gain > 7% of baseline body weight (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism subsection).

8.3 Less Common Clinical Trial Adverse Reactions

Other Adverse Events from Schizophrenia Trials:
Certain portions of the discussion below relating to objective or numeric safety parameters, namely, vital sign changes, weight gain, 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.

Vital Sign Changes:
In placebo-controlled clinical trials, orthostatic hypotension (greater than 30 mm decrease in systolic blood pressure) occurred with an incidence of 5% in oral olanzapine-treated patients compared to 2% in placebo-treated patients (vital sign measurements collected only after 3-7 days of ZYPREXA treatment). Oral olanzapine was associated with a mean baseline to endpoint increase in heart rate of 2.4 beats per minute compared to no change among placebo-treated patients (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular subsection).

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.

Other Adverse Events Observed During Clinical Trials with Oral and Intramuscular Olanzapine Across All Indications
The following discussion relates primarily to weight gain changes observed during clinical trials across all indications.

Weight Changes:
Weight gain has been very commonly observed in olanzapine-treated patients during clinical trials. In 13 placebo-controlled olanzapine monotherapy studies, 22.2% of olanzapine-treated patients gained ≥ 7% of their baseline body weight versus 3% of placebo-treated patients, with a median exposure to event of 8 weeks; 4.2% of olanzapine-treated patients gained ≥ 15% of their baseline weight versus 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline body mass index (BMI) categories.

In long-term studies (at least 48 weeks), both the magnitude of weight gain and the proportion of olanzapine-treated patients who had clinically significant weight gain were greater than in short-term studies. The percentage of patients who gained ≥ 25% of their baseline body weight with long-term exposure was very common (≥ 10%).

Prolactin:
In controlled clinical trials (up to 12 weeks), elevations in prolactin were observed in 30% of olanzapine-treated patients as compared to 10.5% of placebo-treated patients. In the majority of these patients, the elevations were mild. In patients with schizophrenia, menstrual-related adverse events potentially associated with prolactin elevations [1] were common (< 10% to ≥ 1%), whereas sexual function-related and breast-related adverse events were infrequent (< 1% to ≥ 0.1%). In patients treated for other mental illnesses[2], sexual function-related adverse events (erectile dysfunction, libido decreased, loss of libido, orgasm abnormal) potentially associated with prolactin elevations were common (< 10% to ≥ 1%), whereas breast-related and menstrual-related adverse events were infrequent (< 1% to ≥ 0.1%).

Vital Sign Changes:
Bradycardia was uncommonly observed in clinical trials.

Photosensitivity Reactions:
Photosensitivity reactions were uncommonly observed in clinical trials.
Table 4 summarizes core adverse drug reaction terms and their frequencies identified from an integrated database of 42 completed olanzapine clinical studies in adults, consisting of 7787 patients exposed to olanzapine in placebo- or comparator-controlled clinical studies.

Table 4: Core Adverse Drug Reactions from Clinical Trials of Olanzapine

Body System/Adverse Reaction Term	**Frequency**				
	≥ 10%	**< 10% and ≥ 1%**	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**	**< 0.01%**
Body as a Whole					
Pyrexia		X			
Cardiovascular					
[1]Orthostatic Hypotension	X				
Digestive System					
Abdominal Distension			X		
Musculoskeletal System					
Arthralgia		X			

[1] *TEAEs analysis up to 52 weeks of treatment*
[2] *Bipolar Depression, Psychotic Depression, Borderline Personality Disorder and Bipolar Mania*

Body System/Adverse Reaction Term	Frequency				
	≥ 10%	< 10% and ≥ 1%	< 1% and ≥ 0.1%	< 0.1% and ≥ 0.01%	< 0.01%
Nervous System					
Amnesia			X		
Respiratory, Thoracic and Mediastinal Disorders					
Epistaxis			X		
Laboratory Analytes					
Clinical Chemistry					
[1]Alkaline phosphatase –Increased		X			
[1]Gamma Glutamyltransferase (GGT) (U/L) - High		X			
[1]Uric Acid (µmol/L) – High		X			
Hematology					
[1]Leukopenia, including Neutropenia		X			

[1] As assessed by measured values within the clinical trial database.

Dose-Dependent Adverse Events:

Dose-relatedness of adverse events was assessed using data from a clinical trial with a fixed dosage range. Table 5 enumerates the treatment-emergent adverse events in which there was a statistically significantly increasing dose response in this clinical trial.

Table 5: Schizophrenia Trials: Dose-Dependent Adverse Events in a Fixed Dosage Range, Placebo-Controlled Clinical Trial[1] of Oral Olanzapine

	Percentage of Patients Reporting Event			
Body System/ Adverse Event	**Placebo (N = 68)**	**ZYPREXA 5 ± 2.5 mg/day (N = 65)**	**ZYPREXA 10 ± 2.5 mg/day (N = 64)**	**ZYPREXA 15 ± 2.5 mg/day (N = 69)**
Digestive System				
Constipation	0%	6.2%	9.4%	14.5%
Nervous System				
Abnormal dreams	0%	0%	1.6%	4.3%
Dizziness	2.9%	7.7%	9.4%	17.4%
Somnolence	16.2%	20.0%	29.7%	39.1%
Respiratory System				
Pharyngitis	1.5%	3.1%	1.6%	10.1%

[1] Fungal dermatitis was also reported with a statistically significantly increasing dose response, but is not included as a drug cause was remote.

Table 6 enumerates the treatment-emergent adverse events from one 8-week, randomized, double-blind, fixed-dose trial comparing 10 (N = 199), 20 (N = 200) and 40 (N = 200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder. Statistically significant differences among the 3 dose groups were observed for the following safety outcomes: fatigue, dizziness, prolactin elevation, and weight gain (mean change).

Table 6: Schizophrenia Trial: Dose-Dependent Adverse Events in a Fixed Dose, Placebo-Controlled Clinical Trial of

Oral Olanzapine[1]

Adverse Event	ZYPREXA 10 mg/day (N = 195)	ZYPREXA 20 mg/day (N = 191)	ZYPREXA 40 mg/day (N = 197)
Fatigue[2,3] (% reporting event)	1.5%	2.1%	6.6%
Dizziness[3] (% reporting event)	2.6%	1.6%	6.6%
Prolactin Elevation[2,3,4] (% reporting event)	31.2%	42.7%	61.1%
Prolactin Elevation[2,3] (mean change from baseline to endpoint)	-10.5 ng/mL	-1.7 ng/mL	4.9 ng/mL
Weight Gain ≥ 7% at any time (% reporting event)	14.0%	18.4%	20.5%
Weight Gain[2] (mean change from baseline to endpoint)	1.9 kg	2.3 kg	3.0 kg

1 Study HGLF: 8-week, Phase IV, parallel, randomized, double-blind, fixed-dose study in patients with schizophrenia and schizoaffective disorder evaluating the dose-response efficacy and safety of olanzapine 10, 20, and 40 mg/day. Patients were titrated up to their randomized dose over 2 weeks.

2 significant difference between 10 vs. 40 mg/day

3 significant difference between 20 vs. 40 mg/day

4 > 24.2 ng/mL (female) or > 18.77 ng/mL (male) at any time during the trial

Incidence of Treatment-Emergent Extrapyramidal Symptoms:

Table 7 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 oral olanzapine at 3 fixed dosage ranges with placebo in the treatment of schizophrenia.

Table 7: Schizophrenia Trials: Treatment-Emergent Extrapyramidal Symptoms Assessed By Rating Scales Incidence In A Fixed Dosage Range, Placebo-Controlled Clinical Trial -- Acute Phase[1]

	Percentage of Patients			
	Placebo	ZYPREXA 5 ± 2.5 mg/day	ZYPREXA 10 ± 2.5 mg/day	ZYPREXA 15 ± 2.5 mg/day
Parkinsonism[2]	15%	14%	12%	14%
Akathisia[3]	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.

Table 8 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 oral olanzapine at 3 fixed dosage ranges with placebo in the treatment of schizophrenia. Similar results were found during the long-term (up to 1-year) double-blind monotherapy extension bipolar maintenance trial comparing ZYPREXA with placebo; there was a higher statistical incidence of akathisia for combined doses of ZYPREXA versus placebo.

Table 8: Schizophrenia Trials: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in an Oral Fixed Dosage Range, Placebo-Controlled Clinical Trial -- Acute Phase[1]

	Percentage of Patients Reporting Event			
Extrapyramidal Symptoms	**Placebo (N = 68)**	**ZYPREXA 5 ± 2.5 mg/day (N = 65)**	**ZYPREXA 10 ± 2.5 mg/day (N = 64)**	**ZYPREXA 15 ± 2.5 mg/day (N = 69)**
Dystonic events[2]	1%	3%	2%	3%
Parkinsonism events[3]	10%	8%	14%	20%
Akathisia events[4]	1%	5%	11%[1]	10%[1]
Dyskinetic events[5]	4%	0%	2%	1%
Residual events[6]	1%	2%	5%	1%
Any extrapyramidal event	16%	15%	25%	32%[1]

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, opisthotonos, torticollis.

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

The following Table 9 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to three injections during the trials (see 14 CLINICAL TRIALS section). Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection. There were no statistically significant differences from placebo.

*Table 9: Treatment-Emergent Extrapyramidal Symptoms Assessed By Rating Scales Incidence In A Fixed Dose, Placebo-Controlled Clinical Trial Of Intramuscular Olanzapine For Injection In Agitated Patients With Schizophrenia**

	Percentage of Patients				
	Placebo	**Olanzapine IM 2.5 mg**	**Olanzapine IM 5 mg**	**Olanzapine IM 7.5 mg**	**Olanzapine IM 10 mg**
Parkinsonism[1]	0	0	0	0	3
Akathisia[2]	0	0	5	0	0

* 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 10 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia. There were no statistically significant differences from placebo.

*Table 10: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

	Percentage of Patients Reporting Event				
	Placebo (N = 45)	**Olanzapine IM 2.5 mg (N = 48)**	**Olanzapine IM 5 mg (N = 45)**	**Olanzapine IM 7.5 mg (N = 46)**	**Olanzapine IM 10 mg (N = 46)**
Dystonic events[1]	0	0	0	0	0
Parkinsonism events[2]	0	4	2	0	0
Akathisia events[3]	0	2	0	0	0
Dyskinetic events[4]	0	0	0	0	0
Residual events[5]	0	0	0	0	0
Any extrapyramidal event	0	4	2	0	0

* No statistically significant differences.

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

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

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

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

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

Other Investigational Trials

Cerebrovascular Adverse Events (CVAEs) in Elderly Patients with Dementia

Data from 5 placebo-controlled trials in elderly patients with dementia-related psychosis (Alzheimer's, vascular, and mixed; ZYPREXA n = 1178 and placebo n = 478) suggest that there was a higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo (1.3% vs. 0.4%, respectively). Although the incidence of CVAE was not significantly different when analyzed with Fisher's Exact Test (p = 0.177), the difference was found to be significant when simultaneously controlling for age, gender, and type of dementia using Poisson Regression (p = 0.0428). Four patients died in the ZYPREXA group versus 1 patient in the placebo group. In open-label safety trials studied for up to 59 weeks in dementia patients (N = 231), 7 cases of CVAEs, including 2 fatalities, were reported (see 7 WARNINGS AND PRECAUTIONS section).

Data from these trials suggest that patients with a dementia diagnosis of vascular or mixed type had a 5-fold higher likelihood of experiencing CVAEs than patients with a diagnosis of Alzheimer's. There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with ZYPREXA or all antipsychotic agents.

ZYPREXA is not approved for use in elderly patients with dementia.

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In five placebo-controlled trials with oral ZYPREXA in this population, the incidence of mortality was 3.5 % for ZYPREXA -treated patients compared to 1.5% for placebo-treated patients. ZYPREXA is not indicated in elderly patients with dementia.

Adverse Events in Adolescent Patients (ages 13-17 years)

ZYPREXA is not indicated for pediatric use, including adolescent patients (ages 13-17).

The types of adverse events observed in adolescent patients treated with olanzapine were similar to those seen in adult patients. Although no clinical trials designed to compare adolescents to adults were conducted, the data from the adolescent trials were compared to those of the adult trials.

Mean increase in weight in adolescents (4.6 kg over 3 weeks median duration of exposure) was greater than in adults (2.6 kg over 7 weeks median duration of exposure).

In long-term studies (at least 24 weeks), both the magnitude of weight gain and the proportion of adolescent olanzapine-treated patients who had clinically significant weight gain were greater than in short-term studies and were greater than in adult patients with comparable exposures. With long-term exposure, approximately half of adolescent patients gained ≥ 15% and almost a third gained ≥ 25% of their baseline body weight. Among adolescent patients, mean weight gain was greatest in patients who were overweight or obese at baseline.

Sedation-related events are more common in adolescents (44%) as compared to adults (29%).

Core Adverse Drug Reactions and Frequencies from Clinical Trials in Adolescent Patients (ages 13-17 years)

Table 11 summarizes core adverse drug reaction terms for olanzapine compared to placebo and their frequencies identified only during clinical trials in adolescent patients (ages 13 to 17 years).

Table 11: Core Adverse Drug Reactions and Frequencies from Clinical Trials in Adolescent Patients (ages 13-17 years)

Body System/Adverse Reaction Term	Olanzapine		Placebo	
	Frequency	N	Frequency	N
Body as a Whole				
Weight gain ≥ 7% of baseline body weight (kg)[2]	40.6%	197	9.8%	112
Weight gain ≥15% of baseline body weight (kg)[3]	7.1%	197	2.7%	112
Digestive System				
Dry Mouth	6.15%	179	0%	89
Increased Appetite	24%	179	6%	89
Nervous System				
Sedation[1]	44.1%	179	9%	89

1 Represented cluster of MedDRA terms including: hypersomnia, lethargy, sedation, somnolence.

2 Median duration of exposure to event = 4 weeks

3 Median duration of exposure to event = 19 weeks

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Lipids:
In placebo-controlled clinical trials of up to 12 weeks in duration, olanzapine-treated patients had a greater mean increase in fasting total cholesterol, LDL cholesterol, and triglycerides compared to placebo-treated patients.

Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline. However, for mean changes in fasting triglycerides, the difference between olanzapine and placebo was greater in patients with evidence of lipid dysregulation at baseline. Elevations in fasting triglyceride levels ≥ 11.3 mmol/L were uncommonly observed with olanzapine use (8 week median duration of exposure).

Table 12: Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	**Olanzapine***	**Placebo**
Triglycerides: fasting normal to high (< 1.70 mmol/L to ≥ 2.26 mmol/L)	9.2% (N = 457)	4.4% (N = 251)
Triglycerides: fasting borderline to high (≥ 1.70 mmol/L and < 2.26 mmol/L to ≥ 2.26 mmol/L)	39.3% (N = 135)	20.0% (N = 65)
Cholesterol-Total: fasting normal to high (< 5.18 mmol/L to ≥ 6.22 mmol/L)	2.8% (N = 392)	2.4% (N = 207)
Cholesterol-Total: fasting borderline to high (≥ 5.18 mmol/L and < 6.22 mmol/L to ≥ 6.22 mmol/L)	23.0% (N = 222)	12.5% (N = 112)
LDL cholesterol: fasting normal to high (< 2.59 mmol/L to ≥ 4.14 mmol/L)	0% (N = 154)	1.2% (N = 82)
LDL cholesterol: fasting borderline to high (≥ 2.59 mmol/L and < 4.14 mmol/L to ≥ 4.14 mmol/L)	10.6% (N = 302)	8.1% (N = 173)

* Median duration of exposure 8 weeks.

For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism subsection).

The proportion of patients who had changes in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Treatment-emergent clinically significant changes in fasting lipids were observed in patients with or without evidence of dyslipidemia at baseline.

Glucose
In clinical trials (up to 52 weeks) olanzapine was associated with a greater mean change in glucose relative to placebo.

The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or who met criteria suggestive of hyperglycemia), and these patients had a greater increase in HbA1c compared to placebo.

In patients with baseline normal fasting glucose levels (< 5.5 mmol/L), 2.2% (N = 543) of those treated with olanzapine (median exposure duration of 8 weeks) were found to have high glucose levels (≥ 6.99 mmol/L) during olanzapine treatment versus 3.4% (N = 293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥ 5.5 mmol/L and < 6.99 mmol/L), 17.4% (N = 178) of those treated with olanzapine (median exposure duration of 5 weeks) were found to have high glucose levels (≥ 6.99 mmol/L) during olanzapine treatment versus 11.5% (N = 96) of those treated with placebo.

The proportion of patients who had a change in glucose level from normal or borderline at baseline to high increased over time. Treatment-emergent clinically significant changes in fasting glucose were observed in patients with or without evidence of glucose dysregulation at baseline.

Glycosuria was commonly reported in olanzapine-treated patients during clinical trials.

Other Laboratory Changes

Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT (see 7 WARNINGS AND PRECAUTIONS, Hepatic subsection). Olanzapine is also associated with generally mild increases in serum prolactin, which usually decreases with continued drug treatment. Olanzapine is also associated with asymptomatic elevations of eosinophils and uric acid (see 7 WARNINGS AND PRECAUTIONS, Renal subsection), and with decreases in serum bicarbonate.

In 5 double-blind, placebo controlled clinical trials of elderly patients with dementia-related psychosis (n = 1184 total in the olanzapine arms and n = 478 total in placebo arms), olanzapine-treated patients showed significantly greater incidence rates compared to placebo-treated patients of low albumin (10.4% vs 5.5%, respectively), low hemoglobin (4.2% vs 1.8%) and low hematocrit (4.6% vs 2.4%). Of patients who had low albumin values, 3.6% in the olanzapine-treated group vs 1.4% in the placebo-treated also experienced a treatment-emergent respiratory infection. A causal relationship between the two adverse events has not been determined.

Mean increases in fasting glucose were similar in adolescents and adults treated with olanzapine; however, the difference between olanzapine and placebo groups was greater in adolescents compared to adults.

In long-term studies (at least 24 weeks), changes in glucose from normal at baseline to high were uncommon (< 1% and ≥ 0.1%).

Mean increases in fasting total cholesterol, LDL cholesterol, and triglycerides were generally greater in adolescents than in adults treated with olanzapine. However, in short term trials, the differences between olanzapine and placebo were similar for adolescents and adults.

The proportion of treatment-emergent clinically significant changes in normal-to-high or borderline-to-high fasting total cholesterol, LDL cholesterol and triglycerides was greater in adolescents compared to adults, and the differences between olanzapine and placebo in these categories of laboratory values were also generally greater in adolescents. In long-term studies, treatment-emergent clinically significant changes in total cholesterol, LDL cholesterol, and triglycerides were observed in adolescents with or without evidence of dyslipidemia at baseline.

Compared with adults, adolescents treated with olanzapine experienced a significantly higher incidence of elevated prolactin levels (47% in olanzapine-treated adolescents vs 30% in olanzapine-treated adults) and significantly higher mean increases in prolactin levels.

Hepatic aminotransferase elevations (3 times the Upper limit of Normal) are more common in adolescents (12.1%) as compared to adults (5.4%).

Table 13 Adverse Drug Reactions related to Clinical Chemistry and their Frequencies from Clinical Trials in Adolescent Patients (ages 13-17 years)

Clinical Chemistry				
ALT/SGPT > 3X ULN all randomized patients with ALT baseline <= 3X ULN[1]	12.1%	174	2.3%	87
AST/SGOT – Increased[2]	27.6%	163	3.8%	79
Total bilirubin –Decreased[3]	22.1%	154	6.7%	75

GGT – Increased[4]	10.1%	169	1.2%	83
Prolactin – Increased[5]	47.4%	116	6.8%	59
Cholesterol – total, fasting normal to high (< 4.40 mmol/L to ≥ 5.18 mmol/L)[6]	6.9%	87	2.3%	43
Cholesterol – total, fasting borderline to high (≥ 4.40 mmol/L and < 5.18 mmol/L to ≥ 5.18 mmol/L)[6]	38.9%	36	7.7%	13
LDL cholesterol: fasting normal to high (< 2.85 mmol/L to ≥ 3.37 mmol/L)	5.1%	98	4.5%	44
LDL cholesterol: fasting borderline to high (≥ 2.85 mmol/L and < 3.37 mmol/L to ≥ 3.37 mmol/L)	48.3%	29	0%	9
Triglycerides, fasting normal to high (< 1.02 mmol/L to > 1.47 mmol/L)[6]	26.9%	67	10.7%	28
Triglycerides, fasting borderline to high (≥ 1.02 mmol/L and ≤ 1.47 mmol/L to > 1.47 mmol/L)[6]	59.5%	37	35.3%	17
Glucose, fasting normal to high (< 5.55 mmol/L to ≥ 6.99 mmol/L)[6]	0%	124	1.9%	53
Glucose, fasting borderline to high (≥ 5.55 mmol/L and < 6.99 mmol/L to ≥ 6.99 mmol/L)[7]	14.3%	14	0%	13

[1] Covance reference ranges:

		Low	High
(U/L)	Female 13 - ≤ 17.999	6	34
(U/L)	Male 13 - ≤ 17.999	6	43

[2] Covance reference ranges:

		Low	High
(U/L)	Female 13 - ≤ 17.999	10	40
(U/L)	Male 13 - ≤ 17.999	10	40

[3] Covance reference ranges:

		Low	High
(mmol/L)	Female 13 - ≤ 17.999	3	21
(mmol/L)	Male 13 - ≤ 17.999	3	21

[4] Covance reference ranges

		Low	High
(U/L)	Female 13 - ≤ 17.999	0	33
(U/L)	Male 13 - ≤ 17.999	0	51

[5] Covance reference ranges for prolactin as published by Wiedemann and Jonetz-Mentzel (1993)

Female:	12 to 14 years:	2.52 – 16.90 ng/mL
	14 to 19 years:	4.20 – 39.00 ng/mL
Male:	12 to 14 years:	2.84 – 24.00 ng/mL
	14 to 19 years:	2.76 – 16.10 ng/mL

[6] Median duration of exposure was 3 weeks

[7] Median duration of exposure was 5 weeks

Health Canada has not authorized an indication for pediatric use.

8.5 Post-Market Adverse Reactions

Table 14 summarizes core adverse drug reaction terms and their frequencies identified from global post-marketing surveillance in addition to what was reported in clinical trials (*see* preceding section 8 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). A causal relationship between ZYPREXA and the emergence of these events

has not been established.

Table 14: Core Adverse Drug Reactions Seen with Olanzapine Formulations[1]

Body System/Adverse Reaction Term	**Frequency**				
	≥10%	**<10% and ≥1%**	**< 1% and ≥0.1%**	**< 0.1% and ≥ 0.01%**	**< 0.01%**
Body as a Whole					
Allergic reaction[2]					X
Discontinuation reaction[3]					X
Cardiovascular					
Venous Thromboembolism, including Pulmonary Embolism and Deep Vein Thrombosis					X
Digestive System					
Pancreatitis					X
Salivary Hypersecretion[8]			X		
Hematologic					
Thrombocytopenia[4]					X
Hepatobiliary disorders					
Hepatitis				X	
Jaundice					X
Hepatic failure					X
Metabolic					
Diabetic Coma					X
Diabetic Ketoacidosis[5]					X
Hypercholesterolemia[7]					X
Hyperglycaemia				X	
Hypertriglyceridemia[6,7]					X
Exacerbation of pre-existing diabetes				X	
Musculoskeletal System					
Rhabdomyolysis					X
Nervous System					
Restless Legs Syndrome (RLS)[8]			X		
Seizures				X	
Stuttering[1, 9]			X		
Skin and Appendages					
Alopecia					X

Body System/Adverse Reaction Term	Frequency				
	≥10%	<10% and ≥1%	< 1% and ≥0.1%	< 0.1% and ≥ 0.01%	< 0.01%
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)					X
Rash				X	
Urogenital System					
Priapism					X
Urinary Incontinence					X
Urinary Retention					X
Laboratory Analytes					
Clinical Chemistry					
Total bilirubin –Increased					X

[1] Adverse event identified from spontaneous post-marketing surveillance.

[2] e.g., maculopapular rash, anaphylactoid reaction, angioedema, pruritus, or urticaria.

[3] i.e., diaphoresis, nausea or vomiting.

[4] Including a case of thrombocytopenic purpura.

[5] COSTART term is diabetic acidosis.

[6] COSTART term is hyperlipemia.

[7] Random cholesterol levels of ≥6.22 mmol/L and random triglyceride levels of ≥11.30 mmol/L have been very rarely reported.

[8] Adverse event identified from spontaneous post-marketing reporting with frequency determined using the olanzapine clinical trial database.

[9] Stuttering was only studied in oral formulations and the review did not include details about the rapid IM formulation.

As with other atypical anti-psychotics, there have been isolated post-market reports with olanzapine of serious cardiovascular-related adverse events, including fatalities (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting ZYPREXA and then periodically throughout treatment.

Venous Thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including ZYPREXA. However, since patients who require treatment with antipsychotics often present with acquired risk factors for VTE all possible risk factors of VTE e.g., immobilization, should be identified and preventative measures undertaken.

Patients should be advised of the risk of severe constipation during ZYPREXA treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

Atypical antipsychotic drugs, including ZYPREXA, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnea, ZYPREXA should be prescribed with caution.

Risks of somnambulism (sleep walking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including olanzapine.

Cases of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and hyponatremia have been identified during the post-marketing period.

9. DRUG INTERACTIONS

9.2 Drug Interactions Overview

The metabolism of olanzapine may be affected by inhibitors or inducers of the P450 cytochrome isoforms, specifically CYP1A2 activity. Olanzapine clearance was increased by smoking or carbamazepine coadministration. Smoking and carbamazepine therapy are known to induce CYP1A2 activity. Known potent inhibitors of CYP1A2 activity may decrease olanzapine clearance. Olanzapine is not a potent inhibitor of CYP1A2 activity. The pharmacokinetics of theophylline, a drug principally metabolized by CYP1A2, are not altered by olanzapine.

9.3 Drug-Behaviour Interactions

Alcohol: Given the primary CNS effects of ZYPREXA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol since additive pharmacological effects such as increased sedation may occur.

Smoking: Concomitant smoking may induce the metabolism of olanzapine.

9.4 Drug-Drug Interactions

The drugs listed in this Table 15 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 15: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Activated Charcoal	CT	The concomitant administration of activated charcoal reduced the oral bioavailability of ZYPREXA by 50% to 60%.	Activated charcoal may be a useful agent to reduce olanzapine absorption in situations of overdose (see 5 OVERDOSE).
Antacids, e.g. aluminium, magnesium	CT	No effect	Single doses of antacid (aluminium, magnesium) did not affect the oral bioavailability of ZYPREXA.
Antihypertensive Agents	T	N/A	Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents. Caution should be exercised in patients who receive medicinal products that can induce hypotension, bradycardia, or respiratory depression.
Carbamazepine	CT	Olanzapine Cmax, AUC, and t½ were consistently lower when given after carbamazepine.	Concomitant carbamazepine therapy may induce the metabolism of olanzapine.
Cimetidine	CT	No effect	Single doses of cimetidine did not

Proper/Common name	Source of Evidence	Effect	Clinical comment
			affect the oral bioavailability of ZYPREXA.
CYP1A2 Inducers	In vitro	Population modeling has suggested that clearance of olanzapine correlates with the activity of CYP1A2.	Agents that induce CYP1A2 such as omeprazole may increase clearance of olanzapine.
CYP1A2 Inhibitors, e.g. fluvoxamine, ciprofloxacin, ketoconazole	CT	Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC was 52% and 108%, respectively.	A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.
Diazepam	CT	No effect	In clinical trials with single doses of oral ZYPREXA, no inhibition of the metabolism of diazepam (P450 CYP3A4) was evident.
Dopamine Agonists, Levodopa Agonists	T		As it exhibits *in vitro* dopamine antagonism, ZYPREXA may antagonize the effects of levodopa and dopamine agonists.
Drugs Metabolized via P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A	In vitro	In *in vitro* studies with human microsomes, olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A (see 10 CLINICAL PHARMACOLOGY).	Olanzapine is thus unlikely to cause clinically important drug-drug interactions mediated through the metabolic routes described. However, the possibility that olanzapine may alter the metabolism of other drugs, or that other drugs may alter the metabolism of olanzapine, should be considered when prescribing ZYPREXA.
Fluoxetine	CT	Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a mean 16% increase in the maximum concentration of olanzapine and a 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
Imipramine/Desipramine	CT	No effect	In clinical trials with single doses of oral ZYPREXA, no inhibition of the metabolism of imipramine/desipramine (P450-

Proper/Common name	Source of Evidence	Effect	Clinical comment
			CYP2D6) was evident.
Lithium or Biperiden	CT	No effect	Oral ZYPREXA showed no interaction when co-administered with lithium or biperiden.
Lorazepam	CT	In a clinical pharmacokinetic/ pharmacodynamic study, administration of intramuscular lorazepam (2 mg) one hour following intramuscular olanzapine (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. Administration of intramuscular lorazepam two hours after injection of intramuscular olanzapine however, added to the somnolence observed with either drug alone.	Concomitant injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended (see 7 WARNINGS AND PRECAUTIONS).
Theophylline	CT	No effect	The pharmacokinetics of theophylline, a drug principally metabolized by CYP1A2, were not altered by olanzapine in a clinical trial with single doses of IV theophylline.
Valproate	In vitro	Studies in *vitro* using human liver microsomes showed that olanzapine has little potential to inhibit the glucuronidation of valproate, which is the major metabolic pathway. Furthermore, valproate was found to have little effect on the metabolism of olanzapine in vitro. Daily concomitant *in vivo* administration of 10 mg olanzapine for 2 weeks did not affect steady state plasma concentrations of valproate.	Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.
Warfarin	CT	No effect	In clinical trials with single doses of oral ZYPREXA, no inhibition of the metabolism of warfarin (P450 CYP2C9) was evident.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Absorption of olanzapine is not affected by food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been identified.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been identified.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ZYPREXA (olanzapine), a thienobenzodiazepine, is an antipsychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited affinities for serotonin 5HT2A/C, 5HT3, 5HT6; dopamine D1, D2, D3, D4, D5; muscarinic M1-5; adrenergic α1; and histamine H1 receptors.

10.2 Pharmacodynamics

Pharmacodynamic Properties:
Olanzapine displays high receptor affinity binding *in vitro* at dopamine D_2, D_3, D_4 (Ki = 11-31 nM), 5-$HT_{2A/C}$ (Ki = 4 and 11 nM, respectively), 5-HT_3, 5-HT_6, muscarinic M_1-M_5 (Ki = 1.9-2.5 nM), adrenergic α_1 (Ki = 19 nM), and histamine H_1 (Ki = 7 nM) receptor subtypes, while displaying a lower affinity at dopamine D_1 and D_5 receptor subtypes (Ki = 51-119 nM). In a behavioural paradigm predictive of antipsychotic activity, olanzapine reduced conditioned avoidance response in rats at doses lower than 4 times those required to produce catalepsy. In a single dose (10 mg) PET study in healthy subjects, olanzapine produced higher 5-HT_{2A} than dopamine D_2 receptor occupancy. The percent of D_2 occupancy was less than the threshold value predictive of extrapyramidal events.

In animals olanzapine has been observed to produce a significant reduction in the firing of A10 dopaminergic cells. The number of spontaneously active A9 neurons either remained constant or was increased. This may explain the low incidence of extrapyramidal side effects with olanzapine usually associated with the typical antipsychotics.

Olanzapine also increases extracellular levels of dopamine in a regionally specific manner in the prefrontal cortex, similar to mood stabilizers, lithium and valproate.

In Vitro Receptor Binding Affinities:
The binding affinities of olanzapine versus clozapine and haloperidol are summarized in *Table 16*. The binding profile of olanzapine has similarities to that produced by clozapine, although the affinity of olanzapine is somewhat greater for dopamine D_1 and D_2 receptors and lower at 2 receptors. With respect to 5-HT receptor subtypes, both agents show greatest affinity for 5-HT_{2A} and 5-HT_{2C} receptors. The ratio of activity between 5-HT_{2A} and D_2 receptors is slightly less for olanzapine than for clozapine, although olanzapine is still about twice as active at 5-HT_{2A} receptors compared with D_2 receptors. Both compounds also have a high affinity for muscarinic receptor subtypes, particularly the m_1 site. The affinity constants (Ki, nM) for olanzapine, clozapine, and haloperidol are shown below:

Table 16: Affinity constants for olanzapine, clozapine, and haloperidol

Compound	Dopamine D_1	Dopamine D_2	α_1	α_2	Histamine H_1
Olanzapine	31 ± 0.7	11 ± 2	19 ± 1	230 ± 40	7 ± 0.3

Compound	Dopamine D_1	Dopamine D_2	α_1	α_2	Histamine H_1
Clozapine	85 ± 0.7	125 ± 20	7 ± 4	8 ± 3	6 ± 2
Haloperidol	25 ± 7	1 ± 0.04	46 ± 6	360 ± 100	3630 ± 85

Compound	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2C}	5-HT_3
Olanzapine	>10,000	1355 ± 380	800 ± 190	4 ± 0.4	11 ± 1	57
Clozapine	770 ± 220	1200 ± 170	980 ± 115	12 ± 3	8 ± 0.8	69
Haloperidol	7930 ± 500	>10,000	6950 ± 950	78 ± 22	3085	>1000

Compound	m_1	m_2	m_3	m_4	m_5
Olanzapine	1.9 ± 0.1	18 ± 5	25 ± 2	13 ± 2	6 ± 0.8
Clozapine	1.9 ± 0.4	10 ± 1	14 ± 1	18 ± 5	5 ± 1.2
Haloperidol	1475 ± 300	1200 ± 180	1600 ± 305	>10,000	Not Tested

Olanzapine has no significant activity at $GABA_A$, benzodiazepine, or β receptors. Olanzapine also interacts with dopamine D_4 receptors (Ki 27 nM).

In vivo biochemical studies were conducted to confirm the binding data and investigate the functional consequences of interacting with these neurotransmitter receptor sites.

In Vivo Neuroendocrine Studies:
It has been shown that corticosterone concentrations in rats can be elevated by 5-HT-mediated or dopamine-mediated mechanisms. Olanzapine antagonizes the 5-HT (quipazine-induced) (ED_{50} 0.57 mg/kg) and D_2 dopamine receptor-mediated (pergolide-induced) (ED_{50} 3 mg/kg) increases in corticosterone. These results show that olanzapine has greater activity at 5-HT compared with D_2 dopamine receptors *in vivo*. These results complement the behavioural studies showing that olanzapine preferentially antagonizes a 5-HT-induced response.

In Vivo Behavioural Pharmacology:
In behavioural studies, olanzapine exhibits a broad pharmacologic profile, as predicted from the biochemical data.

Olanzapine blocks apomorphine induced climbing behaviour with an ED50 of approximately 5 mg/kg. The climbing response has previously been shown to require both D1 and D2 receptor activation. These results therefore indicate that olanzapine possesses dopamine antagonist activity in vivo.

A second study in mice looked at the ability of olanzapine to block 5 hydroxytryptophan (5 HTP) induced head twitches, a test probably mediated by 5 HT2 receptors. Olanzapine produced dose related reductions in the head twitch response with approximate ED50s of 2 mg/kg. Olanzapine preferentially blocks the head twitch, compared with the climbing response, demonstrating that this agent exhibits greater activity at the 5 HT receptor compared with dopamine receptors in vivo. These results agree with those reported in rats, showing that olanzapine preferentially antagonizes 5 HT mediated rather than dopamine mediated elevations in corticosterone (Moore et al. 1993).

Olanzapine doses of 2.5 to 10 mg/kg produced a significant reduction in oxotremorine induced tremor in mice,

with an ED50 of 3 mg/kg. These results demonstrate that olanzapine possesses anticholinergic activity in vivo at doses which also antagonize dopamine mediated effects.

Inhibition of a conditioned avoidance response has been widely used as a test to predict the antipsychotic potential of a compound, while the induction of catalepsy in rats is associated with the occurrence of extrapyramidal symptoms in the clinic. ED50s for the various compounds in blocking a conditioned avoidance response or inducing catalepsy in rats are given in Table 17.

Table 17 Effect of Olanzapine and Haloperidol on Conditioned Avoidance Responding (CAR) and the Induction of Catalepsy (CAT) in Lister Hooded Rats

Compound	**CAR**	**CAT**	**Ratio**
Olanzapine	5.6 (4.6-6.8)	23 (18.7-29)	4.1
Haloperidol	0.28 (0.24-0.33)	0.74 (0.6-0.9)	2.6

Note: The results are expressed as ED50 values (mg/kg p.o.) with 95% confidence intervals stated in parentheses. The ratio is the ED50 CAT / ED50 CAR.

Although olanzapine induces catalepsy, this only occurs at doses higher than those required to block the conditioned avoidance response.

A number of reports have shown that the "atypical" agent, clozapine, differs from "typical" antipsychotics in its effects on schedule controlled behaviour. In a rat or pigeon conflict test, olanzapine, clozapine, and chlordiazepoxide produced the characteristic changes in rates of responding associated with anxiolytics, although the effect of olanzapine and clozapine was smaller than that seen with chlordiazepoxide. All three compounds decreased or had no effect on the high rates of responding produced in the reward component, whereas the rates in time out and particularly the conflict period were increased. This type of profile was not seen with the "typical" antipsychotic, haloperidol, which only decreased the rates in all the components. These data further emphasize the "atypical" profile of olanzapine.

In Vivo Electrophysiology:
“Typical” antipsychotic agents, such as haloperidol, reduce the spontaneous firing of both A9 and A10 dopaminergic neurons in the CNS following chronic dosing. The A9 (nigrostriatal system) is thought to mediate extrapyramidal motor disturbances, while the A10 (mesolimbic system) has been associated with the antipsychotic activity of compounds. Olanzapine (10 and 20 mg/kg subcutaneously for 21 days) produced a significant reduction in the firing of A10 dopaminergic cells. The number of spontaneously active A9 neurons either remained constant or was increased. These results are very similar to those reported previously for clozapine and further emphasize the “atypical” pharmacologic profile of olanzapine.

Human Versus Animal Metabolism:
In animal species (mice, rats, and dogs) used for toxicologic evaluation, olanzapine was metabolized through aromatic hydroxylation (forming phenolic metabolites and/or their glucuronide conjugates), allylic (alkyl) oxidation, N dealkylation, and N oxidation reactions.

Although similarities in the metabolic fate of olanzapine in animals (mice, rats, and dogs) and humans include the 2 alkyl hydroxylation, N dealkylation, and N oxidation pathways, two significant differences can be noted. First, direct glucuronidation, producing mainly 10 N glucuronide and to a lesser extent 4’ N glucuronide, was a significant metabolic pathway in humans. These N glucuronides were absent in animal species except for a trace amount of 10 N glucuronide in dog urine. Second, metabolites resulting from aromatic oxidation were not found in any human biological fluids. The monkey also did not appear to form 10 N glucuronide, but was similar to humans in apparently not forming metabolites resulting from the oxidative attack of the benzene ring of olanzapine.

10.3 Pharmacokinetics

In the following Table 18, a summary of clinically relevant pharmacokinetic parameters for Olanzapine can be found.

Table 18: Summary of Olanzapine Pharmacokinetic Parameters in Healthy Subjects

Statistic	$t_{½}$ (h)	CL (L/h)	Vd (L)
Number of observations	491	491	479
Mean	**33.1**	**26.1**	**1,148**
Median	**30.5**	**23.6**	**1,091**
5th Percentile	20.7	12.0	660
95th Percentile	54.1	46.9	1,792
Minimum	14.5	7.1	400
Maximum	79.5	142.0	2,438

CL, Plasma Clearance; $t_{1/2}$, Elimination Half-Life; Vd, Volume of Distribution.
Estimates of Olanzapine pharmacokinetic parameters were pooled selectively across 15 clinical pharmacology studies (single dose studies only) comprising a total of 193 subjects.

Oral Administration:

Table 19: Olanzapine Key Pharmacokinetics

Patient Characteristics	Half-Life (hours)	Plasma Clearance (L/hr)
Nonsmoking	38.6	18.6
Smoking	30.4	27.7
Female	36.7	18.9
Male	32.3	27.3
Elderly (65 and older)	51.8	17.5
Non-elderly	33.8	18.2

Although smoking status, gender, and, to a lesser extent, age may affect olanzapine clearance and half-life, the magnitude of the impact of these single factors is small in comparison to the overall variability between individuals.

Absorption:

ZYPREXA is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food.

Distribution:

Plasma concentrations of orally administered olanzapine were linear and dose proportional in trials studying doses from 1 to 20 mg. The maximum plasma concentrations (C_{max}) of olanzapine after single oral doses of 5, 10 and 15 mg averaged 7, 14, and 21 ng/mL, respectively (20 ng/mL = 0.064 µM). In young healthy volunteers, after once-a-day repeated dosing, steady-state C_{max} was approximately twice that achieved after a single dose (e.g., 23 ng/mL versus 12 ng/mL for a 10-mg dose). In the elderly, the steady state plasma concentration was approximately 3-fold higher than that achieved after a single dose (e.g., 16 ng/mL versus 5 ng/mL for a 5-mg dose). In both, young and elderly, steady-state concentrations of olanzapine were obtained after seven days of once daily dosing.

Over time and dosage range, pharmacokinetic parameters within an individual are very consistent. However, plasma concentrations, half-life and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see 7.1 Special Populations). Data from pooled, single dose pharmacokinetic studies showed the half-life of olanzapine to range from 21 to 54 hours (5^{th} to 95^{th} percentile), and the apparent plasma clearance to range from 12 to 47 L/hr (5^{th} to 95^{th} percentile).

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/mL. Olanzapine is bound predominantly to albumin and α_1-acid glycoprotein.

Metabolism:

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which is pharmacologically inactive and does not pass the blood brain barrier. Cytochrome P450 isoforms CYP1A2 and CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. Both metabolites exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

In vitro microsomal studies show that olanzapine is a weak inhibitor of CYP1A2 (Ki = 36 µM), CYP2D6 (Ki = 89 µM), and CYP3A4 (Ki = 490 µM). Based upon these Ki values, little inhibition of these cytochrome P-450 enzymes is expected *in vivo* at concentrations below 5 µM (roughly 1500 ng/mL) because the olanzapine concentration will be less than 10% of its Ki value. In clinical studies, observed steady-state plasma concentrations of olanzapine are rarely > 150 ng/mL (approximately 0.5 µM). Olanzapine is thus not likely to cause clinically important pharmacokinetic drug-drug interactions mediated through the metabolic routes outlined above. (See 9 DRUG INTERACTIONS section).

Pharmacokinetic studies demonstrate that ZYPREXA tablets and ZYPREXA ZYDIS dosage forms of olanzapine are bioequivalent. ZYPREXA ZYDIS orally disintegrating tablets can be used as an alternative to ZYPREXA tablets (see 14.2 Comparative Bioavailability Studies).

Elimination:

After oral administration to healthy subjects, the mean terminal elimination half-life was 33 hours (21 to 54 hours for 5^{th} to 95^{th} percentile) and the mean olanzapine plasma clearance was 26 L/hr (12 to 47 L/hr for the 5^{th} to 95^{th} percentile). Olanzapine pharmacokinetics varied on the basis of smoking status, gender, and age.

Intramuscular Administration:
ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. The peak concentration is on average 4 to 5 fold higher than that of an equivalent oral dose. Area under the curve achieved after an intramuscular dose is equivalent to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are quantitatively similar and qualitatively identical to metabolic profiles after oral administration.

Special Populations and Conditions
Geriatrics: 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 4 DOSAGE AND ADMINISTRATION section).

Sex: 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.

Ethic Origin: In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in olanzapine pharmacokinetics among the three populations. Cytochrome P450 isoform CYP2D6 status does not affect the metabolism of olanzapine.

Hepatic Insufficiency: No differences in the single-dose pharmacokinetics of oral olanzapine were noted in subjects with clinically significant cirrhosis (who were mostly smokers) when compared to healthy subjects (all non-smokers). Multiple-dose studies in patients with hepatic impairment, however, have not been performed.

Renal Insufficiency: There was no significant difference in mean elimination half-life or olanzapine plasma clearance between subjects with severely impaired renal function compared to individuals with normal renal function. Approximately 57% of radio-labelled olanzapine is excreted in urine, principally as metabolites.

11. STORAGE AND STABILITY

ZYPREXA Tablets:
Store tablets at 15°C-30°C. Protect from light and moisture.

ZYPREXA ZYDIS:
Sensitive to light, keep tablets in the original package in a dry place at 15°C-30°C.

ZYPREXA IntraMuscular:
Store ZYPREXA IntraMuscular (unconstituted) between 15°C-30°C.

Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature 20°C-25°C [See USP] for up to 1 hour if necessary.

As with all parenteral drug products, reconstituted solutions should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. **Discard any unused portion of reconstituted ZYPREXA IntraMuscular.**

12. SPECIAL HANDLING INSTRUCTIONS

ZYPREXA Zydis:
ZYPREXA Zydis should be handled carefully with dry hands.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

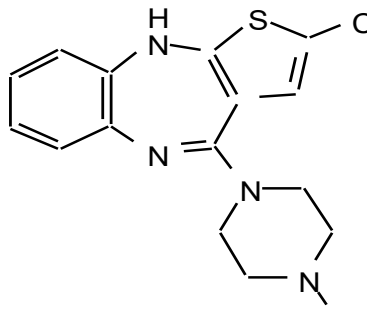
Drug Substance

Non-proprietary name of the drug products: Olanzapine

Chemical name: 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5] benzodiazepine

Molecular formula and molecular mass: $C_{17}H_{20}N_4S$
312.44

Structural formula:



Physicochemical properties:

Description:	Olanzapine is an antipsychotic agent of the thienobenzodiazepine class. It is a yellow crystalline solid, which is soluble in n-Propanol and practically insoluble in water.
pKa:	5.00 and 7.40 in Dimethylformamide/Water (60:40, v/v)
Melting Point:	195 ± 2° C

14. CLINICAL TRIALS

14.1 Efficacy and safety studies

ORAL ADMINISTRATION STUDIES

Schizophrenia and Related Disorders Trials

The efficacy of oral ZYPREXA (olanzapine) in the reduction of and maintenance of the reduction of the manifestations of schizophrenia and related psychotic disorders was established in 3 well-controlled clinical trials of psychotic inpatients who, at entry met the DSM-III-R criteria for schizophrenia (most with a course at entry of 'chronic with acute exacerbation') and 1 well-controlled clinical trial of psychotic inpatients and outpatients who, at entry, met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Study designs for the studies mentioned above and in section 4814.2 can be found in Table 20.

Table 20: Schizophrenia and Related disorder trials characteristics: oral administration

Parameter	1	2	3	4	5
Number of subjects	335	152	431	1996	894
Duration of study	6 weeks	6 weeks	6 weeks	6 weeks	Extension maintenance trials with median treatment length of 237 days
Treatment arms	3 fixed dosage ranges: 5 ± 2.5 mg/day 10 ± 2.5 mg/day 15 ± 2.5 mg/day	2 fixed dose ranges: 1 mg/day 10 mg/day	3 fixed dose ranges: 1 mg/day 5 ± 2.5 mg/day 10 ± 2.5 mg/day 15 ± 2.5 mg/day	1 dosage range: 5 to 20 mg/day	See Studies 1, 3, and 4
Type of control	Haloperidol 15 ± 5 mg/day BID, Placebo	Placebo	Haloperidol 15 ± 5 mg/day BID	Haloperidol 5 to 20 mg/day	Controlled
Further characteristics	-	-	-	2:1 randomization	Double-blinded; extension maintenance trials of studies 1, 3, and 4

Bipolar Disorder Trials

Bipolar Mania:

The efficacy of oral olanzapine in treating acute bipolar mania was demonstrated in 5 controlled studies, including 2 placebo-controlled studies, 2 active comparator studies and 1 cotherapy study. All patients enrolled in these studies had a diagnosis of bipolar I disorder and displayed an acute manic or mixed episode (with or without psychotic features) according to the DSM-IV criteria based on clinical assessment and confirmed by the structured clinical interview for the diagnostic and statistical manual, SCID-P. Study designs for the studies mentioned above and in section 14.2 can be found in

Table 21.

Table 21: Bipolar Mania Trials characteristics: oral administration

	Placebo-controlled trials		Active Comparator trials		Cotherapy trial
Parameter	**1**	**2**	**3**	**4**	**5**
Number of subjects	Y-MRS: 70 LOCF: 69	Y-MRS: 60 LOCF:55	Olanzapine arm: 125 Divalproex arm: 126	Olanzapine arm: 234 Haloperidol arm: 219	Olanzapine + Valproate or Lithium: 229 Valproate or Lithium alone: 115
Duration of study	3 weeks	4 weeks	3 weeks (continuation phase 11 months)	6 weeks (6 weeks maintenance of response phase in the absence of a placebo arm)	6 weeks (18 months re-randomized phase)
Treatment arms	Dose range: 5 to 20 mg/day	Dose range: 5 to 20 mg/day	Dose-range Olanzapine: 5 to 20 mg/day Dose-range Divalproex: 500 to 2500 mg/day	Dose-range Olanzapine: 5 to 20 mg/day Dose-range Haloperidol: 3 to 15 mg/day	Cotherapy vs. Monotherapy
Type of control	Placebo	Placebo	Divalproex	Haloperidol	Monotherapy
Further characteristics	-	-	Double-blinded, Randomized	Double-blinded	Double-blinded

INTRAMUSCULAR ADMINISTRATION STUDIES

The efficacy of intramuscular olanzapine for the rapid control of agitation was established in 3 short-term (up to 24 hours of IM treatment) placebo-controlled trials. Two trials were in agitated inpatients with schizophrenia, schizophreniform disorder and schizoaffective disorder who were able to give informed consent, and included a single active comparator treatment arm of haloperidol injection. One trial was in agitated patients with mania associated with bipolar disorder, and included a single active comparator treatment arm of lorazepam injection. Patients needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication; and (2) exhibiting a level of agitation that met or exceeded a threshold score of > 14 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least one individual item score > 4 using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). The PANSS Excited Component has been validated in non-agitated and agitated patients, and is an established factor of the PANSS. The primary efficacy measure used for assessing agitation was the change from baseline in the PANSS Excited Component at 2 hours after the initial injection. Several additional efficacy measures including the Agitation Calmness Evaluation Scale (ACES), Corrigan Agitated Behaviour Scale (CABS) were also utilized. Patients could receive up to three injections during the 24 hour IM treatment periods; however, patients could not receive a second injection until after the primary efficacy measure was assessed (2 hours following initial injection). The study design of the studies mentioned above can be found in Table 22.

Table 22: Agitated inpatients: intramuscular administration study

Parameter	**1**	**2**	**3**
Number of subjects	270	311	201
Duration of study	24 hours	24 hours	24 hours
Treatment arms	2.5 mg to 10 mg	Olanzapine arm: 10 mg Haloperidol arm: 7.5 mg	Olanzapine arm: 1 to 3 injections (10 mg, 10 mg and 5 mg)

			Lorazepam arm: 1 to 3 injections (2 mg, 2 mg and 1 mg)
Type of control	Placebo	Haloperidol, Placebo	Lorazepam, Placebo
Further characteristics	-	Randomized	Randomized

14.2Study results

ORAL ADMINISTRATION

Schizophrenia and Related Disorders Trials Results

(1) A 6-week, placebo-controlled trial (N = 335) compared 3 fixed dosage ranges of ZYPREXA (5 ± 2.5, 10 ± 2.5, and 15 ± 2.5 mg/day QD), 1 dosage range of haloperidol (15 ± 5 mg/day on a BID schedule), and placebo. The 2 higher dosage ranges of ZYPREXA were statistically significantly superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total, the Clinical Global Impressions - Severity of Illness (CGI - S) scale, and the BPRS positive psychosis cluster. The highest dosage range of ZYPREXA was statistically significantly superior to placebo and to haloperidol on the Scale for the Assessment of Negative Symptoms (SANS). Efficacy of ZYPREXA generally increased with dose. The 5 ± 2.5 mg/day dosage range of ZYPREXA was numerically, but not statistically, significantly superior to placebo on BPRS total and other assessments of overall psychopathology.

(2) A 6-week, placebo-controlled trial (N = 152) compared 2 fixed doses of ZYPREXA (1 or 10 mg/day QD) and placebo. ZYPREXA, 10 mg/day, was statistically significantly superior to placebo on the BPRS total, the BPRS positive psychosis cluster, the CGI-S scale, the Positive and Negative Syndrome Scale (PANSS) total, the PANSS positive subscale, and the PANSS negative subscale. ZYPREXA, 1 mg/day, appeared to be a no-effect dose with no difference, clinically or statistically, from placebo on any assessment of psychopathology.

(3) A 6-week, dose comparison trial (N = 431) compared 3 fixed dosage ranges of ZYPREXA (5 ± 2.5, 10 ± 2.5 and 15 ± 2.5 mg/day QD), ZYPREXA (1 mg/day QD), and haloperidol (15 ± 5 mg/day on a BID schedule). There were no statistically significant differences between groups on efficacy measures except for the highest dosage range of ZYPREXA, which was statistically significantly superior to ZYPREXA, 1 mg, on the BPRS positive psychosis cluster, PANSS positive subscale, and the CGI-S scale.

(4) A 6-week comparator-controlled trial (N = 1996, 2:1 randomization, ZYPREXA: haloperidol) compared 1 dosage range of ZYPREXA (5 to 20 mg/day QD) and 1 dosage range of haloperidol (5 to 20 mg/day QD). The acute mean modal doses (for those patients with at least 3 weeks of treatment) were 13.2 mg/day for ZYPREXA and 11.8 mg/day for haloperidol. ZYPREXA was statistically significantly superior to haloperidol on the BPRS total, the BPRS negative psychosis cluster, the PANSS negative subscale, and the CGI-S scale. ZYPREXA was also statistically significantly superior to haloperidol on the Montgomery-Asberg Depression Rating Scale (MADRS). The validity of this scale in patients with schizophrenia, however, is not established.

(5) The effectiveness of ZYPREXA in long-term therapy, i.e., > 6 weeks, was evaluated in 3 double-blind, controlled, extension maintenance trials (of acute trials 1, 3, and 4 above). Patients who showed adequate clinical improvement following double-blind acute therapy were allowed to continue on in a double-blind, long-term extension maintenance phase on their acute dosage regimen. Long-term maintenance of treatment response (as defined by continued reduction in signs and symptoms sufficient to not require hospitalization for psychosis) was compared over time (894 ZYPREXA-treated patients; median length of treatment was 237 days). The percentage of patients maintaining treatment response over one year was compared. ZYPREXA was statistically significantly superior to placebo in the one placebo-controlled trial and was comparable or statistically significantly superior to the active comparator in 3 of 3 active comparator-controlled trials.

Summary of Schizophrenia and Related Disorders Trials
While the efficacy of ZYPREXA at a dose of 5 mg/day was not statistically superior to placebo (see (1 above)), some individual patients receiving this dose had a good acute response, and were well maintained during a 1-year extension phase.

The above trials (including open-label extension) and an additional trial in geriatric patients with primary degenerative dementia of the Alzheimer's type constitute the primary database (N = 2500 patients treated with ZYPREXA, corresponding to 1122.2 patient-years; N = 810 patients treated with haloperidol, corresponding to 193.0 patient-years; N = 236 patients treated with placebo, corresponding to 27.1 patient-years).

Bipolar Disorder Trials Results
Bipolar Mania:

Placebo-Controlled Trials: The 2 placebo-controlled trials evaluated the efficacy of olanzapine versus placebo in treating bipolar manic or bipolar mixed episodes as measured by the Y-MRS total score LOCF mean change from baseline to endpoint over 3 weeks (n = 70 and n = 69, respectively) and 4 weeks (n = 60 and n = 55, respectively). These trials demonstrated superiority in the efficacy of olanzapine compared with placebo. The key findings were as follows:

- Olanzapine, at a dose range of 5-20 mg/day, was statistically superior to placebo in improving manic symptoms in each study (p = 0.019 and p< 0.001, respectively).
- In each study, a statistically significantly greater percentage of olanzapine-treated patients (48.6% and 64.8%, respectively) compared with placebo-treated patients (24.2% and 42.9%, respectively) responded to treatment (≥ 50% reduction in Y-MRS total score) (p = 0.004 and p = 0.023, respectively).
- In each study, the percentage of patients that were in clinical remission (endpoint Y-MRS total score ≤ 12) were significantly greater among olanzapine patients (45.7% and 61.1%, respectively) compared with placebo patients (25.8% and 35.7%, respectively) (p = 0.020 and p = 0.013, respectively).
- Olanzapine efficacy did not differ significantly among the main subtypes of bipolar mania, for example patients with a history of rapid cycling, with or without psychotic features, and bipolar mixed or bipolar manic.

Active Comparator Trials: Two active comparator trials were conducted.

a) The first active comparator study evaluated the efficacy of olanzapine versus divalproex in treating bipolar manic and bipolar mixed episodes by using the Y-MRS total score LOCF mean change from baseline to endpoint. This study was a 3-week, double-blind study with a double-blind continuation phase of 11 months. The primary objective of the study was to demonstrate non-inferiority in the efficacy of olanzapine compared with divalproex at 3 weeks. Patients were randomized to either olanzapine (5-20 mg/day, n = 125) or divalproex (500-2500 mg/day, n = 126). The key findings were as follows:

- Olanzapine was statistically superior to divalproex in improving manic symptoms as measured by Y-MRS change score at 3 weeks (mean improvements of 13.4 and 10.4 points, respectively, p = 0.028).
- The proportion of patients meeting the criteria for response was not statistically significantly different between olanzapine and divalproex groups (54.4% and 42.3%, respectively) (p = 0.059).
- The proportion of patients that was in clinical remission was significantly greater among olanzapine patients (47.2%) compared with divalproex patients (34.1%) (p = 0.039).

The second active comparator study evaluated the efficacy of olanzapine versus haloperidol in treating bipolar manic or mixed episodes by assessing the proportion of patients in protocol-defined remission from manic and depressive symptoms at 6 weeks. Remission was defined as: 1) achieving improvement in clinical symptomatology in manic and depressive symptoms; 2) having achieved specific reductions in Y-MRS and HAMD-21 total scores; and 3) continuing to take study medication at Week 6. This trial consisted of a 6-week double-blind phase followed by a 6-week double-blind maintenance of response phase in the absence of a placebo arm. Patients were randomly assigned to treatment with olanzapine 5-20 mg/day

(n = 234) or haloperidol 3-15 mg/day (n = 219). The key findings were as follows:

- Olanzapine and haloperidol were similarly effective in improving manic symptoms.
- A clinical response to treatment was defined as a ≥ 50% improvement in Y-MRS total score from baseline to endpoint. In both treatment groups, a large proportion of patients responded to treatment. At the end of the acute phase 72.3% and 74.2% of olanzapine and haloperidol patients, respectively met the response criteria, and at the end of the continuation phase almost all patients were classified as responders (96.3% of 160 olanzapine patients and 94.1% of 136 haloperidol patients).
- The proportion of patients in symptomatic remission at the end of the acute phase (6 weeks) was similar for olanzapine and haloperidol patients (52.1% versus 46.1%, respectively (p = 0.152)). Among patients who entered the continuation phase and were not in symptomatic remission at 6-weeks, significantly more olanzapine patients (68.3%) than haloperidol patients (41.0%) were in remission by the end of the continuation period (p = 0.014).
- Manic symptoms continued to improve among olanzapine patients to a statistically significant extent.
- Olanzapine was statistically significantly more efficacious than haloperidol in patients without psychotic features (acute phase remission rates were 56.7% in 104 olanzapine patients and 41.6% in 89 haloperidol patients, respectively) (p = 0.043).

Cotherapy Trial: This trial evaluated the efficacy of olanzapine plus either valproate or lithium (cotherapy, n = 229) versus valproate or lithium alone (monotherapy, n = 115) in treating bipolar manic or mixed episodes as measured by the Y-MRS total score LOCF mean change from baseline to endpoint. This study was a 6-week, double-blind study with a re-randomized double-blind phase of 18 months. The key findings were as follows:

- Olanzapine in combination with either valproate or lithium was significantly more efficacious than monotherapy (valproate or lithium) in improving manic symptoms (mean improvements of 13.1 and 9.1 points, respectively) (p = 0.003).
- The proportion of patients that clinically responded to treatment was statistically significantly greater among patients receiving olanzapine cotherapy (67.7%) than lithium or valproate monotherapy (44.7%, p < 0.001).
- The percentage of patients that were in clinical remission was significantly greater in the olanzapine cotherapy group (78.6%) compared with the lithium or valproate monotherapy group (65.8%, p = 0.012).
- The difference in time to remission was also statistically significantly different (p = 0.002). The median estimated remission time was 14 days for olanzapine cotherapy-treated patients and 22 days for monotherapy-treated patients.

Bipolar Maintenance:

The efficacy of oral olanzapine as monotherapy for maintenance treatment of bipolar disorder in patients who responded to acute treatment with olanzapine for a manic or mixed episode was demonstrated in two 1-year 'time to event' controlled trials: one placebo-controlled and one active comparator trial against lithium monotherapy.

All patients enrolled in these studies had a diagnosis of bipolar I disorder and displayed an acute manic or mixed episode (with or without psychotic features) according to the DSM-IV criteria.

For both studies: Patients had to meet study-defined response criteria (YMRS total score of ≤ 12 and a HAMD-21 total score ≤ 8) during open-label treatment with olanzapine (or olanzapine plus lithium in the active comparator study) in order to be randomized into the double-blind maintenance period for observation of study-defined relapse. Dosing was flexible (5 - 20 mg/day for olanzapine; serum levels 0.6 - 1.2 mEq/L for lithium).

The exit criteria was symptomatic relapse of bipolar disorder, either mania or depression. Symptomatic relapse of mania was defined as reaching a YMRS total score ≥ 15, and symptomatic relapse of depression as reaching a HAMD-21 total score ≥ 15; for the placebo-controlled study only, the definitions also included being hospitalized

for mania or depression. Thus, the primary efficacy variable was time to, and incidence of, the exit symptomatic relapse of bipolar disorder, based on analysis of Kaplan-Meier time-to-relapse curves. The key characteristics for the bipolar maintenance trials can be found in Table 23.

Table 23: Bipolar Maintenance Trials characteristics: oral administration

Parameter	**1**	**2**
Number of subjects	Olanzapine arm: 225 Placebo arm: 136	Olanzapine + Placebo arm: 217 Lithium + Placebo arm: 214
Duration of study	1 year	1 year
Treatment arms	Dose range: 5 to 20 mg/day	Dose range Olanzapine arm: 5 to 20 mg/day Dose range Lithium arm: 0.6–1.2 mEq/L serum level
Type of control	Placebo	Lithium Monotherapy

1) Placebo-controlled trial:
The study evaluated the efficacy of olanzapine vs placebo in maintenance treatment of manic or mixed bipolar episodes by using survival curve analysis to assess the time to, and incidence of, relapse of bipolar disorder. In this trial, 361 patients who had demonstrated response criteria for an average of 16 days were randomized to either continuation of olanzapine at their same dose (n = 225) or to placebo (n = 136), for observation of relapse for up to one year.

The key findings were as follows:

- Figure 1 shows the 1-year time-to-relapse curves for total discontinuations from the study in each arm over time, whether exiting due to relapse, or withdrawal due to adverse events or other reasons. The percentage of patients remaining in the study (i.e., relapse-free, and have not withdrawn for any reason) can be seen at each of the 3, 6, 9 and 12 month points; at study-end, this is 24% (n = 53) for olanzapine and 10% (n = 13) for placebo. The time-point at which 50% of the patients in a specific arm had withdrawn for any reason was Day 59 for the olanzapine group compared to Day 23 for the placebo group.

- Figure 2 shows the 1-year time-to-relapse curves for specifically the exit criterion of bipolar relapse (i.e., patients who withdrew for other reasons were censored and excluded from the calculated numerators and denominators). Olanzapine was superior to placebo, for both incidence of bipolar relapse (46.7% vs 80.1%, respectively), and median time to relapse (174 days vs 22 days, respectively). Note that a high relapse incidence for the placebo arm is not unexpected given the limited time that patients had been demonstrating response criteria prior to randomization.

- Figures 2a and 2b show the efficacy time-to-relapse curves for each of manic and depressive relapse, respectively. Olanzapine showed a statistically significant advantage over placebo in terms of each of mania and depression, although a greater advantage was seen in mania.

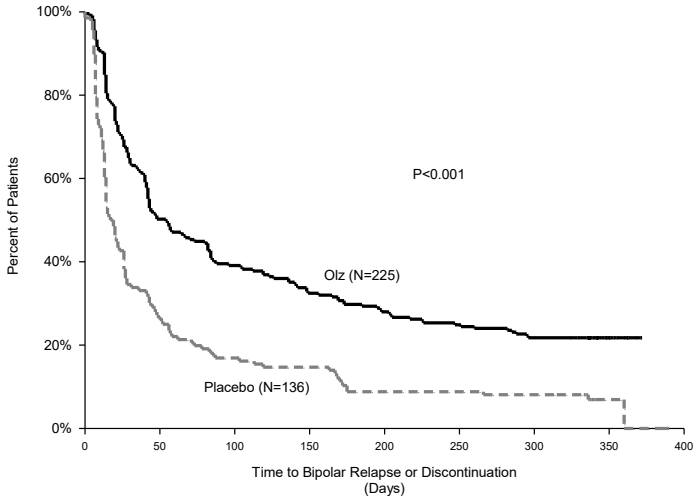


Figure 1:Time to Event (Relapse or Discontinuation)
Study HGHL; Double-Blind Treatment Phase

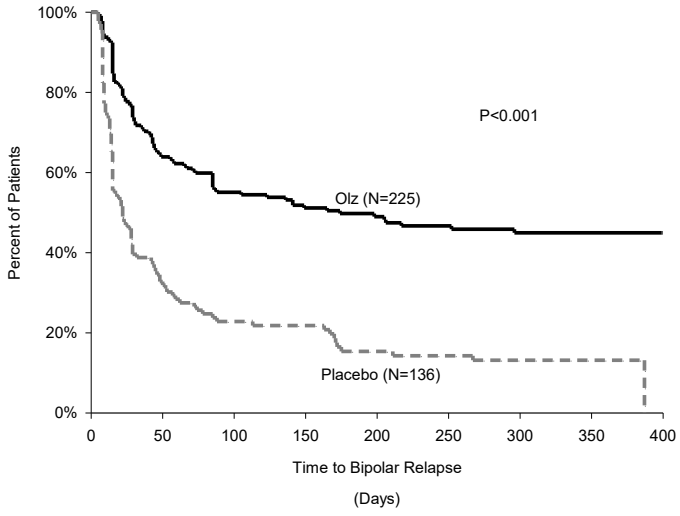


Figure 2:Time to Symptomatic Relapse of Bipolar Disorder, Including Hospitalization
Study HGHL; Double-Blind Treatment Phase

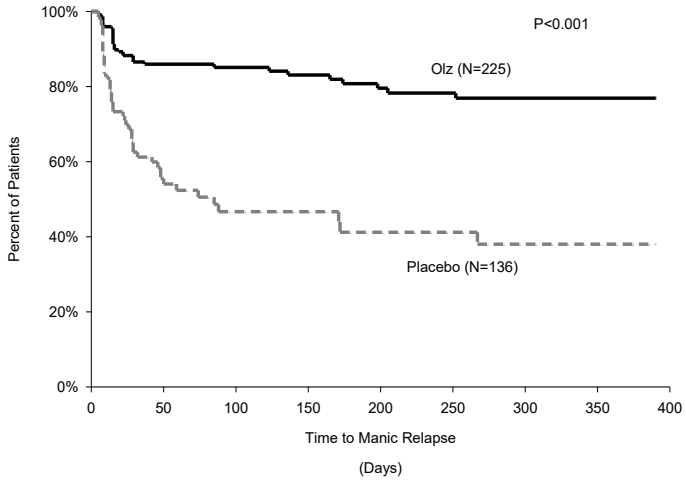


Figure 2a: Time to Symptomatic Relapse of Mania, Including Hospitalization Study HGHL; Double-Blind Treatment Phase

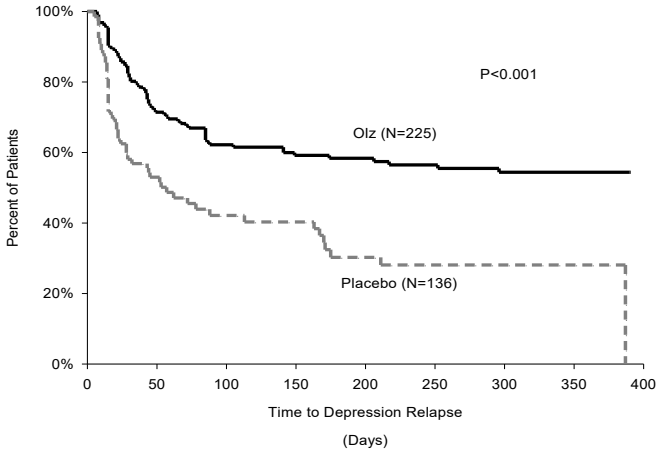


Figure 2b: Time to Symptomatic Relapse of Depression, Including Hospitalization Study HGHL; Double-Blind Treatment Phase

2) Active comparator trial:

The study evaluated the efficacy of olanzapine vs lithium in maintenance treatment of manic or mixed bipolar episodes in a non-inferiority design to assess the incidence of relapse of bipolar disorder and further, by using survival curve analysis to assess time to relapse. In this trial, 543 patients who had demonstrated response criteria for an average of 20 days were randomized to either olanzapine plus placebo (n = 217) or lithium plus placebo (n = 214) for observation of relapse for up to one year. The first month of the double blind period was a taper period to allow for non-abrupt lithium discontinuation. The non-inferiority margin used in this study was: ± 20% of the efficacy seen for the reference population.

The key findings were as follows:

- Figure 3 shows the 1-year time-to-relapse curves for total discontinuations from the study in each arm over time, whether exiting due to relapse, or withdrawal due to adverse events or other reasons. The percentage of patients remaining in the study (i.e., relapse-free, and have not withdrawn for any reason) can be seen at each of the 3, 6, 9 and 12 month points; at study-end, this is 42% (n = 94) for olanzapine and 28% (n = 61) for lithium. The time-point at which 50% of the patients in a specific arm had withdrawn for any reason was Day 255 for the olanzapine group compared to Day 192 for the lithium group.

- Figure 4 shows the 1-year time-to-relapse curves for specifically the exit criterion of bipolar relapse (i.e., patients who withdrew for other reasons were censored and excluded from the calculations of numerators and denominators). Olanzapine was non-inferior to lithium for both incidence of bipolar relapse (30.0% vs 38.8%, respectively), and time to 25% of patients experiencing relapse (122 days vs 143 days, respectively).

- It can be seen from Figure 4 that for approximately the first five months of the 1-year trial, relapse rate was higher in olanzapine-treated patients; thereafter, the rate of relapse for lithium increases, while that for olanzapine flattens out.

- Figures 4a and 4b are the 1-year time-to-relapse curves for each of the exit criterion of manic and depressive relapse respectively. Olanzapine showed a statistically significant advantage over lithium in rate of mania relapse, and was non-inferior for depressive relapse.

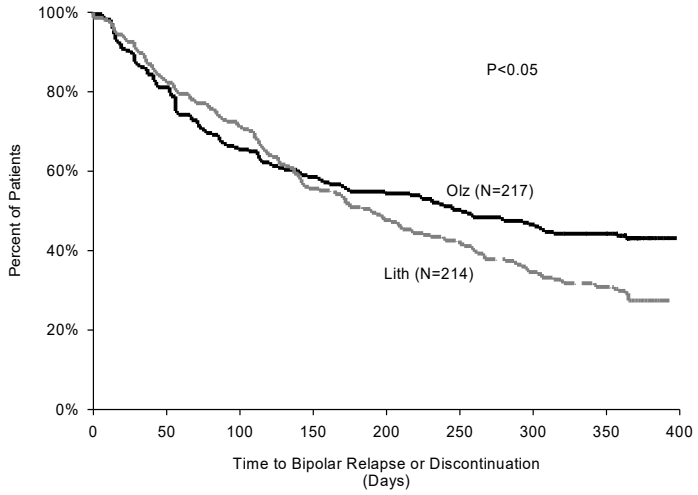


Figure 3:Time to Event (Relapse or Discontinuation)
Study HGHT; Double-Blind Treatment Phase

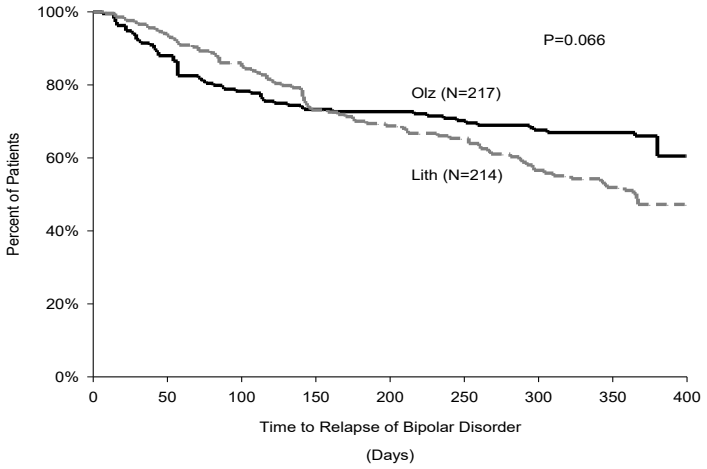


Figure 4:Time to Symptomatic Relapse of Bipolar Disorder
Study HGHT; Double-Blind Treatment Phase

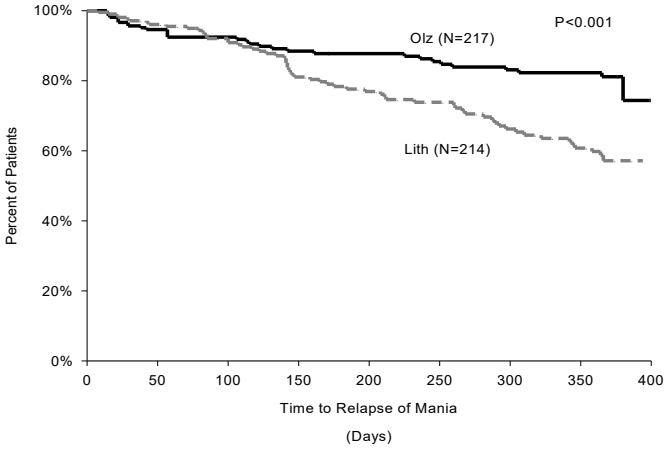


Figure 4a: Time to Symptomatic Relapse of Mania
Study HGHT; Double-Blind Treatment Phase

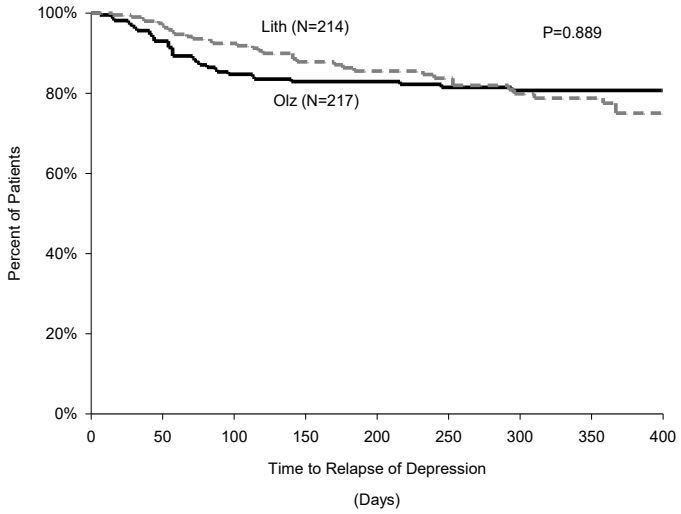


Figure 4b: Time to Symptomatic Relapse of Depression
Study HGHT; Double-Blind Treatment Phase

Summary of Bipolar Disorder Trials

Bipolar Mania: Olanzapine was more efficacious than placebo and divalproex and as effective as haloperidol in improving overall manic symptomatology in patients with acute bipolar I disorder, manic or mixed episode, with or without psychotic symptoms, and with or without a history of rapid cycling. Olanzapine is associated with a faster onset of action (based on median time to remission estimated with Kaplan-Meier analysis) compared to divalproex and similar to that of haloperidol. The addition of olanzapine also improved patients not responding to lithium or valproate. Olanzapine was not associated with inducing or worsening symptoms of depression.

Bipolar Maintenance: Two 1-year controlled studies support the use of ZYPREXA monotherapy in maintenance treatment of bipolar patients who responded to acute ZYPREXA treatment for a manic or mixed episode. Based on analysis of one-year Kaplan-Meier survival curves, olanzapine was superior to placebo, and non-inferior to lithium, in both time to, and incidence of, bipolar relapse over one year.

INTRAMUSCULAR ADMINISTRATION STUDIES Results

In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder (n = 270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were superior to placebo on the PANSS Excited Component and the CABS at 2 hours post-injection. There was a statistically significant dose response relationship over the range of 2.5 mg to 10 mg. The 5 mg, 7.5 mg and 10 mg doses were statistically significantly superior to both placebo and the 2.5 mg dose on the PANSS Excited Component, the CABS, and the ACES. The superior treatment responses on the PANSS Excited Component for the 5 mg, 7.5 mg, and 10 mg doses compared to placebo were observed at 30 minutes post-injection, the first timepoint measured.

The following table shows the number of injections received by patients in each treatment group over the 24 hour treatment period. As can be seen, less than 25% of patients in the olanzapine 10 mg group required more than one injection, compared to 67% in the placebo group.

Table 24: Summary of Injection Frequency

No of Injections	Olanzapine IM 2.5 mg (N = 48)	Olanzapine IM 5.0 mg (N = 45)	Olanzapine IM 7.5 mg (N = 46)	Olanzapine IM 10.0 mg (N = 46)	Haloperidol IM 7.5 mg (N = 40)	Placebo (N = 45)
1	23 (47.9)	29 (64.4)	33 (71.7)	35 (76.1)	30 (75.0)	15 (33.3)
2	22 (45.8)	15 (33.3)	12 (26.1)	10 (21.7)	7 (17.5)	9 (20.0)
3	3 (6.3)	1 (2.2)	1 (2.2)	1 (2.2)	3 (7.5)	21 (46.7)

In a second placebo-controlled trial agitated inpatients meeting DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder (n = 311) were randomized (2:2:1 ratio) to one to three injections of a fixed intramuscular olanzapine for injection dose of 10 mg, intramuscular haloperidol (7.5 mg) or placebo. Olanzapine for injection was superior to placebo on the PANSS Excited Component, the CABS, and the ACES at 2 hours post-injection. The superior treatment response of 10 mg olanzapine for injection compared to placebo on the PANSS Excited Component was observed as early as 15 minutes post-injection, the first timepoint measured. In the olanzapine treatment group 21% of patients received two injections, and 3% three injections during the 24 hour treatment period, compared to 44% and 6% respectively in the placebo treatment group.

(3) In a placebo-controlled trial in acutely agitated patients diagnosed with bipolar I disorder and displaying an acute manic or mixed episode (with or without psychotic features) according to the DSM-IV (n = 201), intramuscular (IM) olanzapine and IM lorazepam were compared. Patients were randomized (2:1:1 ratio) to 1 to 3 injections over 24 hours of IM olanzapine (10 mg, 10 mg and 5 mg), IM lorazepam (2 mg, 2 mg and 1 mg) or IM placebo (3rd injection to patients in the placebo arm was 10 mg IM olanzapine) to a maximum cumulative IM olanzapine dose of 25 mg, or IM lorazepam dose of 5 mg. Olanzapine for injection was superior to IM placebo and IM lorazepam in reducing agitation as measured by change in mean PANSS Excited Component score, the CABS, and the ACES during the 2 hours following injection. The superior treatment response of 10 mg olanzapine for injection compared to lorazepam (2 mg) or placebo on the PANSS Excited Component was observed as early as 30 minutes post-injection, the first time-point measured. In the olanzapine treatment group, 18% of patients received two injections, and 8% three injections during the 24 hour treatment period, compared to 28% and 26% respectively in the lorazepam treatment group, and 12% and 41%, respectively, in the placebo treatment group.

Bioequivalence of the 15 mg and 20 mg tablets to multiple 5 mg tablets has been clearly demonstrated in two separate studies. These tablet formulations are equally well absorbed and can be readily interchanged.

Table 25: Summary Tables of the Comparative Bioavailability Data

	Geometric Mean Arithmetic Mean (CV%)		
PARAMETER	**15 mg Zyprexa Tablet**	**3 x 5 mg Zyprexa Tablet**	**Ratio of Geometric Means (%)**
AUC_{0-t} (ng×hr/mL)	820.0 833.1 (19.1)	841.2 862.3 (23.2)	97.5
AUC_{0-72} (ng×hr/mL)	678.7 690.7 (20.2)	676.6 690.0 (20.7)	100.3
AUC_{0-4} (ng×hr/mL)	875.3 891.5 (20.3)	899.6 925.7 (24.6)	97.3
C_{max} (ng/mL)	21.2 21.6 (19.9)	21.4 21.9 (21.2)	98.9
T_{max}[a] (h)	--- 6.1 (73.4)	--- 5.7 (36.6)	---
T_2[a] (h)	--- 33.7 (20.0)	--- 36.6 (19.1)	---

Study included N = 14 subjects (7/14 females; 12/14 nonsmokers)

[a] The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (CV%).

	Geometric Mean Arithmetic Mean (CV%)		
PARAMETER	**20 mg Zyprexa Tablet**	**4 x 5 mg Zyprexa Tablet**	**Ratio of Geometric Means (%)**
AUC_{0-t} (ng·hr/mL)	522.0 557.6 (37.4)	509.7 538.3 (33.6)	102.4
AUC_{0-72} (ng·hr/mL)	459.4 487.2 (35.5)	446.6 470.4 (32.8)	102.8
AUC_{0-4} (ng·hr/mL)	538.3 574.4 (37.2)	525.4 555.3 (33.6)	102.4
C_{max} (ng/mL)	17.9 18.7 (31.5)	19.5 20.5 (33.0)	91.9
T_{max}[a] (h)	--- 6.1 (42.1)	--- 4.3 (51.3)	---
$T_{½}$[a] (h)	--- 26.5 (17.1)	--- 27.1 (19.0)	---

Study included N = 14 subjects (14/14 males; 14/14 smokers)

[a] The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (CV%).

Pharmacokinetic studies showed that the ZYPREXA Tablets and ZYPREXA ZYDIS dosage forms are bioequivalent. ZYPREXA ZYDIS orally disintegrating tablets can be used as an alternative to ZYPREXA Tablets.

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

An extensive series of acute, subchronic, chronic, reproduction, and genetic toxicity as well as oncogenicity studies

have been conducted to support clinical trials with olanzapine. In most of these studies, olanzapine was given by the oral route to rodents, rabbits, and monkeys in an aqueous suspension with 5% to 10% acacia and to dogs as neat material in capsules.

General Toxicology:

The findings of toxicology studies support the safety of olanzapine for oral use in humans as an antipsychotic agent.

Acute Toxicity:
The acute toxicity of olanzapine was studied in mice, rats, dogs, and monkeys. The estimated median lethal dose for each species is shown below in Table 26.

Table 26: Acute Toxicity Summary

		Estimated Median Lethal Dose (mg/kg/day)	
Species	**Route**	**Males**	**Females**
Mouse	Oral	211	208
Rat	Oral	174	177
Dog	Oral	Both sexes > 100 mg/kg	
Monkey	Nasogastric	Both sexes > 100 mg/kg	
Rat	Intraperitoneal	112	107

Signs of toxicity in rodents included hypoactivity, lethargy, leg weakness, coma, tremors, clonic convulsions, salivation, poor grooming, and depressed body weight gain.

The potential for irritation of an aqueous intramuscular formulation of olanzapine was tested in one *in vitro* and two *in vivo* (dog and rabbit) studies. The intent of these studies was to characterize the effects at the site of injection. Overall, these tests indicated that formulations of olanzapine, at 1.7 to 8.4 mg/mL in a tartaric acid/lactose vehicle, have the potential to cause slight irritation of skeletal muscle. While the *in vitro* model suggested a potential for moderate irritation at the higher concentrations tested, the *in vivo* models indicated either very little or slight potential for irritation.

Long-term toxicity:
Subchronic administration studies of up to 3 months in duration have been conducted by the oral route in mice, rats, and dogs and chronic toxicity studies of up to 1 year were conducted by the oral route in rats and dogs.

The predominant effects in laboratory animals given olanzapine were CNS depression and anticholinergic effects related to the pharmacology of the drug. Tolerance to the CNS depression developed in repeated-dose studies. Depressed body weight gain was a consistent finding in mice given 30 mg/kg/day and in rats given 4 mg/kg/day. Effects on hematology parameters were found in each species studied in repeated-dose studies. Rats given 16 mg/kg/day had decreased lymphocyte and neutrophil counts and atrophy of bone marrow consistent with the marked reduction in body weight gain. Mice given 3 mg/kg/day developed leukopenia, due primarily to lymphocytopenia, but also associated with neutropenia. Lymphoid necrosis of thymus and spleen was seen in mice given ≥ 10 mg/kg/day. Instances of reversible neutropenia, with or without thrombocytopenia, or anemia developed in a low number of individual dogs treated with 8 or 10 mg/kg/day. Bone marrow from some dogs with olanzapine-induced neutropenia responded to olanzapine with lower than expected numbers of maturing granulocytic cells; however, progenitor and proliferating cells were present in adequate numbers. No olanzapine-related hematologic effects were seen in dogs receiving olanzapine at either 2 or 5 mg/kg/day.

Effects observed in rats consistent with increased plasma concentrations of prolactin in rats included decreased

weights of ovaries and uterus. Histopathologic tissue alterations in mammary gland morphology and vaginal epithelium and increased prominence of ovarian follicles were also consistent with elevated prolactin concentrations. Prolactin-induced histopathologic tissue alterations found in rats regressed after treatment cessation. No unexpected toxicologically important findings unrelated to pharmacologic activity were found in the 1-year studies in rats given 4 mg/kg/day or in dogs given 5 mg/kg/day.

Genotoxicity:
Olanzapine was not mutagenic or clastogenic in a full range of standard tests which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests. Appropriate positive controls were used in each test to verify the sensitivity of the test systems.

Carcinogenicity:
The oncogenic potential of olanzapine was evaluated in studies in rats and mice. Carcinogenicity studies were conducted in CD-1 mice and Fischer 344 rats. Olanzapine was administered orally to mice at doses of 3, 10, or 20 mg/kg for 19 months (males) or 21 months (females) in an initial study, and in a subsequent study at doses of 0.5, 2, or 8 mg/kg for 21 months (males and females). Rats received oral doses of 0.25, 1, 2.5, or 4 mg/kg (males) or 0.25, 1, 2.5, 4, or 8 mg/kg (females) for 24 months. Initial dose levels 2.5 and 4 mg/kg/day in females were increased to 4 and 8 mg/kg/day, respectively, on Day 211. These doses are equivalent to 2 to 70 times the maximum daily human dose (mouse studies) or 0.9 to 28 times the maximum daily human dose (rats). A maximum tolerated dose was achieved in both mouse and rat studies. Increased mortality was seen in mice at doses of 10 and 20 mg/kg and decreases in circulating lymphocytes and neutrophils were seen at doses 0.5 mg/kg. In female mice treated with olanzapine, the incidence of mammary tumours was increased at doses ≥ 2 mg/kg. Female rats treated with 4 or 8 mg/kg had an increase in malignant mammary tumours, but the overall incidence of mammary gland neoplasia was unchanged. An increase in total incidence of mammary gland tumours in female mice given 10 or 20 mg/kg/day (the high dose was decreased from 30 mg/kg/day due to excess mortality) was also noted. Antipsychotic drugs, including olanzapine, have been shown to chronically elevate prolactin concentrations in rodents. An increase in mammary neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The role of prolactin in human breast cancer has not been defined conclusively, and there are presently no epidemiologic data indicating increased risk for breast cancer for humans using antipsychotic drugs.

Reproductive and Developmental toxicology:
Fertility studies in male and female rats and teratology studies in rats and rabbits have been conducted by the oral route. Mating performance was affected by administration of olanzapine due to sedation in male rats given doses greater than 18 times the maximum daily human dose, (5 mg/kg/day in rats) but the effect was quickly reversed when treatment stopped. Estrous cycles were affected and reproduction parameters were influenced in rats given doses greater than 4 times the maximum daily human dose (≥ 1 mg/kg/day in rats). No adverse effects were observed on numbers of corpora lutea, implantations, fetal viability, or fetal weight, and there were no effects on litter size or on the survival, growth, or development of the offspring from parents given up to 18 times the maximum daily human dose (5 mg/kg/day in rats). Although the reproductive process in female rats from mating through fertilization was not adversely affected by treatment, this evidence does not exclude a possible interference with maintenance of pregnancy at high doses of olanzapine. Reproduction studies, performed in rats and rabbits at doses of olanzapine 3.5 and 7 times the maximum daily human dose (20 mg), respectively, have revealed no evidence of harm to the fetus. Maternal toxicity, developmental toxicity (indicated by fetal growth retardation and slightly delayed ossification at birth), and increased numbers of nonviable offspring occurred at higher doses (in rats at 14 and 63 times the maximum daily human dose and in rabbits at 28 and 105 times the maximum daily human dose). However, fetal malformations were not increased. Transient modest decreases in activity levels of the progeny from females given 0.25 mg/kg/day and skeletal changes indicative of growth retardation in fetuses from females given 5 mg/kg/day were observed. Transient decreases in offspring activity have occurred at all doses; however, there were no effects on body weight, growth, mating, fertility, or live births in second-generation animals. Placental transfer of olanzapine occurs in rat fetuses. Olanzapine was also detected in the milk of rats at concentrations up to three-fold higher than those in the plasma.

Hematologic Indices:

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs given high doses of olanzapine (24 to 30 times the maximum daily human dose), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia secondary to compromised nutritional status in rats. A few dogs treated with 24 to 30 times the maximum daily human dose developed reversible neutropenia or reversible hemolytic anemia between 1 and 10 months of treatment. Effects on hematology parameters in each species involved circulating blood cells, and no evidence of bone marrow cytotoxicity was found in any of the species examined.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ZYPREXA

(olanzapine tablets)

ZYPREXA ZYDIS

(olanzapine orally disintegrating tablets)

Read this carefully before you start taking **ZYPREXA / ZYPREXA ZYDIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZYPREXA / ZYPREXA ZYDIS**.

Serious Warnings and Precautions

Higher Death Rate in Elderly Patients with Dementia:

- ZYPREXA is not for use in elderly patients with dementia.
- Elderly patients with dementia have a higher death rate when taking ZYPREXA / ZYPREXA ZYDIS and other medicines. Most deaths are caused by serious heart problems, stroke or infections.

Tell your healthcare professional right away if you have sudden weakness or numbness in the face, arms, or legs, and speech or vision problems.

What is ZYPREXA / ZYPREXA ZYDIS used for?

ZYPREXA / ZYPREXA ZYDIS (olanzapine tablets and olanzapine orally disintegrating tablets) is used in adults to treat symptoms of:

- schizophrenia and related psychotic disorders
- bipolar disorder

How does ZYPREXA / ZYPREXA ZYDIS work?
ZYPREXA / ZYPREXA ZYDIS is an antipsychotic medicine. It helps control certain natural chemicals in the brain. This will help control the symptoms of schizophrenia and bipolar mania.

What are the ingredients in ZYPREXA / ZYPREXA ZYDIS?
Medicinal ingredient: olanzapine.

Non-medicinal ingredients of ZYPREXA:
carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, and microcrystalline cellulose.

The colour coating and ink contain some or all of the following ingredients: FD&C Blue No.2 Aluminum Lake, polyethylene glycol, polysorbate 80, Synthetic Red Iron Oxide, titanium dioxide, triacetin.

Non-medicinal ingredients of ZYPREXA ZYDIS:
aspartame, gelatin, mannitol, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA / ZYPREXA ZYDIS comes in the following dosage forms:
ZYPREXA: tablets; 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg.

ZYPREXA ZYDIS: orally disintegrating tablets; 5 mg, 10 mg, 15 mg, and 20 mg.

Do not use ZYPREXA / ZYPREXA ZYDIS if:
• you are allergic to olanzapine or any of the ingredients in ZYPREXA / ZYPREXA ZYDIS or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Zyprexa. Talk about any health conditions or problems you may have, including if you:
- are pregnant or plan to become pregnant
- are breast feeding or plan on breast feeding
- have had an allergic reaction to any medicine which you have taken previously to treat your current condition
- have diabetes or a family history of diabetes
- have a history of any problems with the way your heart beats or have any heart problems
- have a history of stroke or high blood pressure
- have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral birth control.
- are a smoker
- have ever had blackouts or seizures
- drink alcoholic beverages or use drugs
- exercise vigorously or work in hot or sunny places
- have a history of liver problems, hepatitis, or yellowing of the eyes and skin (jaundice)
- have a history of kidney problems
- have prostate or bladder problems
- have intestinal or bowel problems (paralytic ileus)
- have raised pressure within the eye (glaucoma)
- suffer from lactose intolerance because ZYPREXA tablets contain lactose
- cannot take phenylalanine because ZYPREXA ZYDIS contains aspartame, a source of phenylalanine
- have breast cancer
- have pituitary tumours
- have or have a history of sleep apnea
- are 65 years or older

Other warnings you should know about:

Falls: ZYPREXA / ZYPREXA ZYDIS may cause tiredness, low blood pressure and unstable muscle coordination. This may lead to falls and injuries.

Hyperprolactinemia: ZYPREXA / ZYPREXA ZYDIS may cause higher levels of prolactin. You may be at higher risk of breaking a bone if you have high levels of prolactin and a condition called hypogonadism.

Pregnancy, breast-feeding and newborns:
- If you plan to get pregnant, tell your healthcare professional. Your healthcare professional will decide if you should take take ZYPREXA / ZYPREXA ZYDIS.
- If you get pregnant during treatment, tell your healthcare professional immediately. Your healthcare professional will decide if you should continue to take ZYPREXA / ZYPREXA ZYDIS.
- If you take ZYPREXA / ZYPREXA ZYDIS during pregnancy your baby might have the following:
    - difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

Tell your healthcare professional if your newborn baby has these symptoms. Seek emergency hospital care right away if the symptoms are serious. The symptoms may resolve on their own.

Check-ups and monitoring:
You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will:

- Check that your heart is working properly.
- blood tests to check your blood sugar levels, blood fat levels, blood and liver health.
- Monitor your blood pressure.
- Check your body weight

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZYPREXA / ZYPREXA ZYDIS:

- Medicines used to treat anxiety or to help you sleep such as lorazepam
- Medicines used to treat depression or obsessive-compulsive disorder like fluvoxamine
- Medicines used to treat high blood pressure such as metoprolol
- Medicines used to treat stomach problems like omeprazole
- Medicines typically used to treat epilepsy (seizures) such as carbamazepine
- Medicines used to treat fungal infections like ketoconazole
- Medicines used to treat bacterial infections like ciprofloxacin
- Medicines used to treat symptoms in Parkinson's disease like pramipexole or levodopa
- Activated charcoal
- Drinking alcohol
- Smoking

How to take ZYPREXA / ZYPREXA ZYDIS:

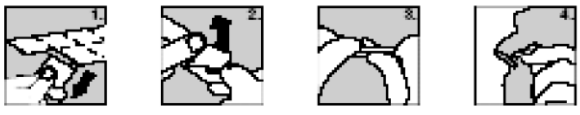
- Always take ZYPREXA / ZYPREXA ZYDIS exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take ZYPREXA / ZYPREXA ZYDIS for as long as your healthcare professional prescribes it. Do not stop taking this medicine unless your healthcare professional tells you to.
- Take your prescribed dose at the same time each day.

Proper Handling Instructions
ZYPREXA:

- Swallow ZYPREXA tablets whole with a glass of water. Taken with or without food.

ZYPREXA ZYDIS:

- Handle ZYPREXA ZYDIS carefully with dry hands.



Follow the instructions below:

1. Separate one blister cell from the strip by tearing along the dotted line.
2. Carefully peel off the backing foil.
3. Gently push the tablet out from the bottom of the blister.
4. Avoid touching the tablet with your hands. Put the tablet directly into your mouth. It will begin to dissolve in your mouth within a few seconds. You can also place the tablet directly into a full glass (125 mL or 4 ounces) of water, milk, coffee, orange juice or apple juice. Stir and drink all of the contents right away.

Usual dose:

ZYPREXA / ZYPREXA ZYDIS (Adults):

- Your healthcare professional will decide the best dose depending on the disease.
- Your healthcare professional will monitor your health. They may interrupt, reduce, increase or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much ZYPREXA / ZYPREXA ZYDIS, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Show the healthcare professional your bottle of tablets. Do this even if there are no signs of discomfort or poisoning.

Missed Dose:

- If you miss a dose of ZYPREXA / ZYPREXA ZYDIS by a few hours, take the dose when you remember.
- If most of the day has passed, wait until your next scheduled dose and try not to miss any more.
- **Do not take 2 doses at once.**

What are possible side effects from using ZYPREXA / ZYPREXA ZYDIS?

These are not all the possible side effects you may have when taking ZYPREXA / ZYPREXA ZYDIS. If you experience any side effects not listed here, tell your healthcare professional:

- drowsiness
- weight gain
- dizziness
- anxiety
- increased appetite
- fluid retention
- constipation
- dry mouth
- a feeling of restlessness (akathisia)
- low blood pressure upon rising from a lying or sitting position
- back pain
- stuttering (disruptive speech)
- increased salivation (salivary hypersecretion)
- memory loss
- breast enlargement in men
- milk secretion, changes in period in women

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Constipation (new or worsening)		✓	

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		✓	
UNCOMMON			
Bradycardia (slow heartbeat)		✓	
RARE			
Hyperglycaemia, Glycosuria (high sugar in blood or urine): Extreme thirst, increased urination, dry mouth, tiredness, visual disturbances, nausea and vomiting, abdominal pain, increased hunger		✓	
Liver problems: fever, yellow skin or eyes, dark urine, weakness, abdominal pain, nausea, vomiting, loss of appetite, itching, light coloured stool, trouble thinking clearly			✓
Low white blood cell count: infection, such as cold, flu-like symptoms, fever, sore throat, as well as weakness or general feeling of unwellness		✓	
Seizures: loss of consciousness with uncontrollable shaking (“fit”)			✓
VERY RARE			
Allergic reactions: skin rash, hives, swelling, difficulty breathing			✓
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch, sudden chest pain, difficulty breathing and heart palpitations		✓	
Neuroleptic Malignant Syndrome (NMS, a nervous system disorder): High fever, muscle rigidity, rapid heartbeat, profuse sweating, irregular pulse			✓
Pancreatitis (pancreas inflammation): severe abdominal pain, fever, nausea, vomiting			✓
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Serious skin reactions: (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]): skin rash or redness developing into widespread rash with blisters and peeling skin, swollen lymph nodes and fever.			✓
Sudden cardiac death (SCD, heart failure): chest pain, shortness of breath, fainting, fast heartbeats			✓
Cerebrovascular adverse events (disturbance of blood flow to the brain), **including stroke**: Sudden weakness or numbness in the face, arms, or legs, and speech or vision problems			✓
Tardive dyskinesia: Muscle twitching or abnormal movements of the face or tongue			✓

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Thrombocytopenia (low blood platelets): bruise easily, excessive bleeding		✓	
Rhabdomyolysis (skeletal muscle break down): Very dark ("tea coloured") urine, muscle tenderness and/or aching			✓
UNKNOWN			
Hyponatremia (low level of sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizures, coma		✓	
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store ZYPREXA / ZYPREXA ZYDIS at 15°C-30°C, in original package, in a dry place. Protect from light.
- Keep out of reach and sight of children.

If you want more information about ZYPREXA / ZYPREXA ZYDIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or CHEPLAPHARM Registration GmbH, Germany or by calling 1-888-XEDITON (933-4866)).

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ZYPREXA IntraMuscular
(olanzapine tartrate for injection)

Read this carefully before you start taking **Zyprexa IntraMuscular** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Zyprexa IntraMuscular.**

Serious Warnings and Precautions

Higher Death Rate in Elderly Patients with Dementia:

- **Zyprexa IntraMuscular** is not for use in elderly patients with dementia.
- Elderly patients with dementia have a higher death rate when taking **Zyprexa IntraMuscular** and other medicines. Most deaths are caused by serious heart problems, stroke or infections.

Tell your healthcare professional right away if you have sudden weakness or numbness in the face, arms, or legs, and speech or vision problems.

What is Zyprexa IntraMuscular used for?
ZYPREXA IntraMuscular (olanzapine tartrate for injection) is used in adults with schizophrenia and related psychotic disorders, and bipolar mania to:

- quickly control agitation

How does Zyprexa IntraMuscular work?
ZYPREXA IntraMuscular is an antipsychotic medicine. It helps control certain natural chemicals in the brain. This will help control agitation in adults with schizophrenia and related psychotic disorders, and bipolar mania.

What are the ingredients in Zyprexa IntraMuscular?
Medicinal ingredient: olanzapine (as olanzapine tartrate).

Non-medicinal ingredients: lactose and tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

Zyprexa IntraMuscular comes in the following dosage forms:
ZYPREXA IntraMuscular: single use vial containing 10 mg olanzapine (as olanzapine tartrate).

Do not use Zyprexa IntraMuscular if:

- you are allergic to olanzapine or any of the ingredients in Zyprexa IntraMuscular

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Zyprexa IntraMuscular. Talk about any health conditions or problems you may have, including if you:

- are pregnant or plan to become pregnant
- are breast feeding or plan on breast feeding
- have had an allergic reaction to any medicine which you have taken previously to treat your current condition
- have diabetes or a family history of diabetes
- have a history of any problems with the way your heart beats or have any heart problems
- have a history of stroke or high blood pressure
- are dehydrated or have low body fluids
- have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity,

recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral birth control.
- are a smoker
- have ever had blackouts or seizures
- drink alcoholic beverages or use drugs
- exercise vigorously or work in hot or sunny places
- have a history of liver problems, hepatitis, or yellowing of the eyes and skin (jaundice)
- have a history of kidney problems
- have prostate or bladder problems
- have intestinal or bowel problems (paralytic ileus)
- have raised pressure within the eye (glaucoma)
- suffer from lactose intolerance because ZYPREXA IntraMuscular contain lactose
- cannot take phenylalanine because Zyprexa IntraMuscular contains aspartame, a source of phenylalanine.
- have breast cancer.
- Have pituitary tumours.
- have or have a history of sleep apnea.
- are 65 years or older.

Other warnings you should know about:

Falls: ZYPREXA IntraMuscular may cause tiredness, low blood pressure and unstable muscle coordination. This may lead to falls and injuries.

Hyperprolactinemia: ZYPREXA IntraMuscular may cause higher levels of prolactin. You may be at higher risk of breaking a bone if you have high levels of prolactin and a condition called hypogonadism.

Hypotension (low blood pressure): ZYPREXA IntraMuscular may cause low blood pressure or fainting. Your healthcare professional will monitor your blood pressure, heart rate and breathing during and after treatment. You may feel dizzy or drowsy after injection. You should lay down after injection until your healthcare professional checks your blood pressure and breathing.

Pregnancy, breast-feeding and newborns:
- If you plan to get pregnant, tell your healthcare professional. Your healthcare professional will decide if you should take take ZYPREXA IntraMuscular.
- If you get pregnant during treatment, tell your healthcare professional immediately. Your healthcare professional will decide if you should continue to take ZYPREXA IntraMuscular.
- If you take ZYPREXA IntraMuscular during pregnancy your baby might have the following:
    - difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

Tell your healthcare professional if your newborn baby has these symptoms. Seek emergency hospital care right away if the symptoms are serious. The symptoms may resolve on their own.

Check-ups and monitoring:
You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will:
- Check that your heart is working properly.
- Do blood tests to check your blood sugar levels, blood fat levels, blood and liver health.
- Monitor your blood pressure and heart rate.
- Check your body weight.

Driving and using machines: ZYPREXA IntraMuscular may cause sleepiness and dizziness. Before you do tasks which may require special attention, wait until you know how you respond to ZYPREXA IntraMuscular.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZYPREXA IntraMuscular:

- Medicines used to treat anxiety or to help you sleep, like benzodiazepines, such as lorazepam
- Medicines used to treat depression or obsessive-compulsive disorder like fluvoxamine
- Medicines used to treat high blood pressure such as metoprolol
- Medicines used to treat stomach problems like omeprazole
- Medicines typically used to treat epilepsy (seizures) such as carbamazepine
- Medicines used to treat fungal infections like ketoconazole
- Medicines used to treat bacterial infections like ciprofloxacin
- Medicines used to treat symptoms in Parkinson's disease like pramipexole or levodopa
- Activated charcoal
- Drinking alcohol
- Smoking

How to take ZYPREXA IntraMuscular:

- ZYPREXA IntraMuscular will be given to you by a healthcare professional in a healthcare setting.
- It will be given to you intramuscularly, by an injection directly into your deep muscle (IM).

Usual dose:
ZYPREXA IntraMuscular (adults):

- Your healthcare professional will decide on the best dose for you based on your general condition and needs.
- Your healthcare professional will monitor your health. They may interrupt, reduce, increase or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.
- Your healthcare professional may also decide to give you other medications depending on your condition and needs.

Overdose:

If you think you, or a person you are caring for, have taken too much ZYPREXA IntraMuscular, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss an appointment, talk to your healthcare professional immediately.

What are possible side effects from using Zyprexa IntraMuscular:
These are not all the possible side effects you may have when taking ZYPREXA IntraMuscular. If you experience any side effects not listed here, tell your healthcare professional.

- drowsiness
- weight gain
- dizziness
- anxiety, hostility
- increased appetite
- fluid retention
- constipation
- dry mouth
- a feeling of restlessness (akathisia)

- decreased blood pressure upon rising from a lying or sitting position
- increased salivation (salivary hypersecretion)

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bradycardia (slow heartbeat)		✓	
Constipation (new or worsening)		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		✓	
RARE			
Hyperglycaemia , Glycosuria (high sugar in blood or urine): Extreme thirst, increased urination, dry mouth, tiredness, visual disturbances, nausea and vomiting, abdominal pain, increased hunger		✓	
Liver problems: fever, yellow skin or eyes, dark urine, weakness, abdominal pain, nausea, vomiting, loss of appetite, itching, light coloured stool, trouble thinking clearly			✓
Low white blood cell count: infection, such as cold, flu-like symptoms, fever, sore throat, as well as weakness or general feeling of unwellness		✓	
Seizures: loss of consciousness with uncontrollable shaking (“fit”)			✓
VERY RARE			
Allergic reactions: skin rash, hives, swelling, difficulty breathing			✓
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch, sudden chest pain, difficulty breathing and heart palpitations		✓	
Neuroleptic Malignant Syndrome (NMS, a nervous system disorder): High fever, muscle rigidity, rapid heartbeat, profuse sweating, irregular pulse			✓
Pancreatitis (pancreas inflammation): severe abdominal pain, fever, nausea, vomiting			✓

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Serious skin reactions: (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]): skin rash or redness developing into widespread rash with blisters and peeling skin, swollen lymph nodes and fever.			✓
Sudden cardiac death (SCD, heart failure): chest pain, shortness of breath, fainting, fast heartbeats			✓
Cerebrovascular adverse events (disturbance of blood flow to the brain), **including stroke**: Sudden weakness or numbness in the face, arms, or legs, and speech or vision problems			✓
Tardive dyskinesia: Muscle twitching or abnormal movements of the face or tongue			✓
Thrombocytopenia (low blood platelets): bruise easily, excessive bleeding		✓	
Rhabdomyolysis (skeletal muscle break down): Very dark ("tea coloured") urine, muscle tenderness and/or aching			✓
UNKNOWN			
Hyponatremia (low level of sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizures, coma		✓	
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by

mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Your healthcare professional will store ZYPREXA IntraMuscular.
  - Store ZYPREXA IntraMuscular (unconstituted) in original package at 15°C-30°C.
  - Reconstituted ZYPREXA IntraMuscular may be stored at 20°C-25°C for up to 1 hour if needed.
  - Any unused portion of the reconstituted ZYPREXA IntraMuscular should be thrown away.
- Keep out of reach and sight

If you want more information about ZYPREXA IntraMuscular:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or CHEPLAPHARM Registration GmbH by calling 1-888-XEDITON (933-4866).

This leaflet was prepared by CHEPLAPHARM Registration GmbH.

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