ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 4189 patients with approximately 2665 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional clinical trials as of May 1, 1997.

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

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

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

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

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

ZY 2226 1117

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

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

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

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

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

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Trials - SCHIZOPHRENIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[1]	8	4
Akathisia	5	1

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

ZY 2226 1119

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 3-Week and 4-Week Trials– BIPOLAR MANIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

ZY 2226 1120

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

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

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

	Percentage of Patients Reporting Event	
	Olanzapine	**Placebo**
Body System/Adverse Event	**(N=532)**	**(N=294)**
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2

ZY 2226 1121

Table 1 (cont.)

Treatment-Emergent Adverse Events:

Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2

ZY 2226 1122

Table 1 (cont.)

Treatment-Emergent Adverse Events:

Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Nervous System (cont.)		
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea[2], hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder[3], rash, thinking abnormal, weight loss.

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

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

ZY 2226 1123

Additional Findings Observed in ~~Premarketing~~ Clinical Trials--The following findings are based on ~~premarketing~~ clinical trials ~~in schizophrenia~~.

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

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

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

	Percentage of Patients			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[1]	15	14	12	14
Akathisia[2]	23	16	19	27

* No statistically significant differences.

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

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

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

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

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

ZY 2226 1124

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

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

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

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

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

Laboratory Changes--An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum

prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

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

In the olanzapine clinical trial database, as of September 30, 1999, olanzapine-treated patients (N=4234) who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 2% of patients. Of these patients, the random elevated glucose levels were found to be transient in 44% of them while they continued to receive olanzapine. Random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 1% of patients. Of these patients, the random elevated glucose levels were found to be transient in 26% of them while they continued to receive olanzapine.

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

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

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

ZY 2226 1126

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

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

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

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

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

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

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

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

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

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

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

Special Senses--*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, corneal lesion, deafness, diplopia, dry eyes, ear pain, eye

hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

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

*Adjusted for gender.

Postintroduction Reports--Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: diabetic coma and priapism.

ZY 2226 1128

Virginia Stauffer
03/08/2000 10:50 PM

To: Robert W Baker/AM/LLY@Lilly, John S Kennedy/AM/LLY@Lilly, Bruce Kinon/AM/LLY@Lilly
cc:
Subject: Unbelievable abstract!

This abstract came up on my alert search this week. This article must have been written by Janssen!! I wonder what

Ginny

Prescrire - Olanzapine - Keep an eye on this neuroleptic
(CANADIAN FAMILY PHYSICIAN, 2000, Vol. 46, 322-326)
Authors:

Olanzapine (Zyprexa(R)), a **neuroleptic,** has obtained marketing authorization for treatment of schizophrenia.

The clinical file is satisfactory, **but in the absence of relevant trials**, it has not yet been demonstrated that olanzapine

The global efficacy of olanzapine was not substantially different from that of haloperidol in two of the three comparative

The **only relevant comparative trial fails to demonstrate the superiority of olanzapine over risperidone.**

Olanzapine has fewer adverse neurologic effects than haloperidol, but there is no evidence that it differs from other re

Olanzapine can have anticholinergic adverse effects and frequently causes weight gain.

Active surveillance is required because subclinical cases of elevated transaminase levels, increased blood pressure, a

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Robert W Baker
03/09/2000 08:48 AM

To: James B Gregory/AM/LLY@Lilly
cc: Jack E Jordan/AM/LLY@Lilly, Allan L Wolford/AM/LLY@Lilly
Subject: Re: Verbatum

Dear Jim:

The verbatum is very attractive. From medical standpoint it may be supportable, depending on how strong the proof needs to be or how convinced we need to be. Bottom line is that Allan and you have done a nice job with this; I'm on board with it for the meeting; might have to tinker if we were presenting in venue that required more airtight scientific support. if necessary, here are the details of my thinking:

Most of the verbatum's elements undoubtedly are correct: Zyprexa has unique properties, it has specific and robust effectiveness for some key symptoms; some of these ssymptoms span two or more disease states; it acts without many adverse actions.

The normalization of critical brain functions is true at a clinical level, e.g., reducing mania; it may be true at a neurochemical level as well, depending on how one defines critical functions.

Finally, the element that is most difficult to nail down is that the unique properties "allow" the specific effectiveness. On its face this must be the case, so I assume that this is appropriate for Jack's presentation. If we had to be more scientific, we could link theoretically our receptor profile to certain therapeutic properties, as we did in the mania medical slide kit. If it came to medically *proving* the connection we'd be out of luck.

Best,

Robert

ZY 2226 1433

Robert W Baker
02/29/2000 02:23 PM

To: Michele Sharp/AM/LLY@Lilly
cc:
Subject: Re: ziprasidone update

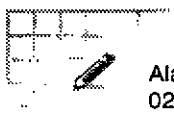
Dear Michele:

I've seen the draft proposal for the PI. Do you have any more elaborate info on glucose/olanzapine available?

Thanks,

Robert

---------- Forwarded by Robert W Baker/AM/LLY on 02/29/2000 02:23 PM ----------



Alan Breier
02/29/2000 02:18 PM

To: Robert W Baker/AM/LLY@Lilly
cc:

Subject: Re: ziprasidone update

Robert,

You may want to get the final glucose data from Michele Sharp. It is most up-to-date and we are considering changing the label to include it.

Alan
Robert W Baker

Robert W Baker

02/29/2000 08:52 AM

To: Alan Breier/AM/LLY@Lilly
cc:

Subject: ziprasidone update

Dear Alan:

Jack Jordan forwarded your call about ziprasidone issues. I understand that it is unofficial, but it is incredibly helpful nonetheless as we work on marketing/blunting strategy, so thanks!

On a different topic, I know that you've been working on the glucose/olanzapine issue. We are having a large "market research" conference with about 200 bipolar high prescribers on March 9. Among other things, I am assigned to discuss weight/glucose, etc. If there is anything that I'm unlikely to know that you view as important/appropriate to communicate, please forward.

Best,

Robert

ZY 2226 1528