Dr. William Wirshing: State of Alaska's Expert

- **"They are among the most powerful disease modifiers in all of medicine.... They are a godsend to most people."**

Tr. 170, Ln. 15-21

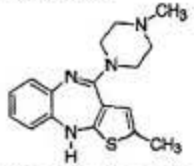
1996 Label – Zyprexa Prescribing Information

PV 2961 AMP

ZYPREXA™
(Olanzapine)

DESCRIPTION

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



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

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 5 mg (16 µmol), 7.5 mg (24 µmol), or 10 mg (32 µmol). Inactive ingredients are carnauba wax, color mixture white, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine $D_{1\text{-}4}$ (K_i=11-31 nM), muscarinic $M_{1\text{-}5}$ (K_i=1.9-25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i > 10 µM).

The mechanism of action of olanzapine, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1\text{-}5}$ receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics:

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately

1996 Zyprexa Label: Weight Gain Information

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:

ZYPREXA™
(Olanzapine)

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Trials

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.

Adverse Reactions:

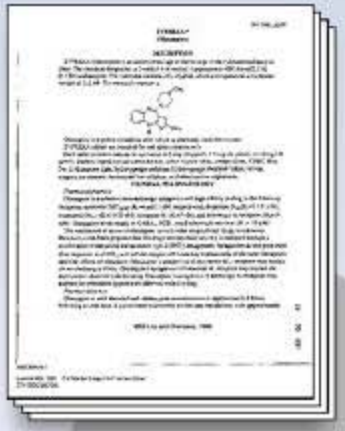
Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials – The most commonly observed adverse events associated with the use of olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that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

* * *

Weight gain: olanzapine = 6%
placebo = 1%

(emphasis added)

1996 Zyprexa Label: Weight Gain Information



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.

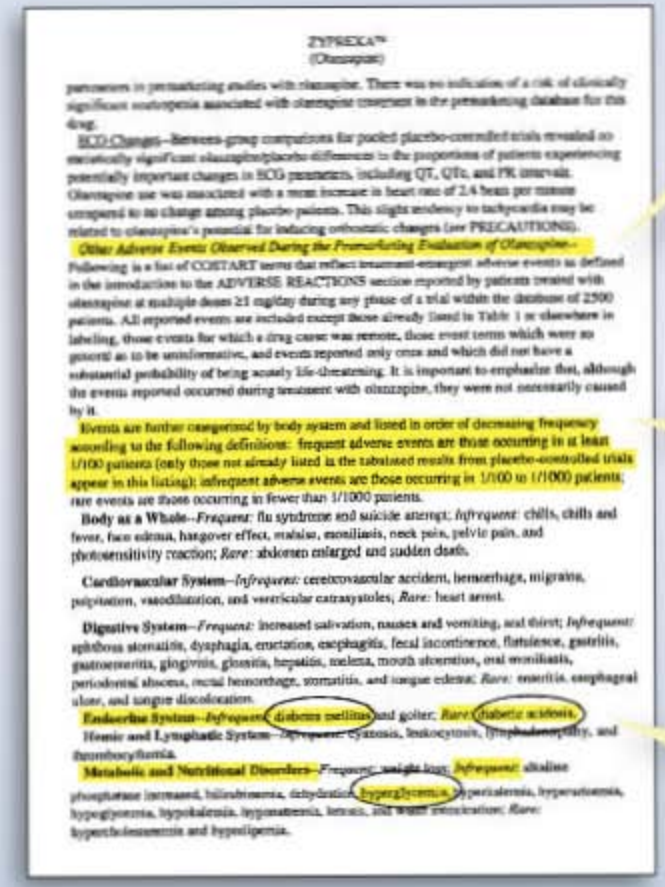
Adverse Reactions:

* * *

During long-term continuation therapy with olanzapine...56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight.

(emphasis added)

1996 Zyprexa Label: Hyperglycemia and Diabetes Information



ZYPREXA™
(Olanzapine)

pancreatitis in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

ECG Changes—Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine 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 Premarketing Evaluation of Olanzapine—Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with olanzapine at multiple doses ≥1 mg/day during any phase of a trial within the database of 2500 patients. All reported events are included except those already listed in Table 1 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 events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events reported occurred during treatment with olanzapine, they were not necessarily caused by it.

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

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

Cardiovascular System—*Infrequent:* cerebrovascular accident, hemorrhage, migraine, palpitation, vasodilation, and ventricular extrasystoles; *Rare:* heart arrest.

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

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

Hemic and Lymphatic System—*Infrequent:* cyanosis, leukocytosis, lymphadenopathy, and thrombocythemia.

Metabolic and Nutritional Disorders—*Frequent:* weight loss; *Infrequent:* alkaline phosphatase increased, bilirubinemia, dehydration, hyperglycemia, hyperkalemia, hypernatremia, hyperglycemia, hypokalemia, hyponatremia, ketosis, and weight increase; *Rare:* hypercholesterolemia and hypolipemia.

Other Adverse Events Observed During the Premarketing Evaluation of Olanzapine

- Frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing)
- Infrequent adverse events are those occurring in 1/100 to 1/1000 patients

Endocrine System – *Infrequent:* diabetes mellitus....

* * *

Metabolic and Nutritional Disorders – ...*Infrequent:*...hyperglycemia....

Medical Letter: Zyprexa – Body Weight Changes

ZYPREXA®--BODY WEIGHT CHANGES

Weight change has been a documented side effect of antipsychotic drug (APD) use for over 30 years[1] and both conventional (i.e., haloperidol and chlorpromazine) and atypical APDs (i.e., risperidone, sertindole, olanzapine, and clozapine) have been shown to be associated with weight changes[2]. Based on clinical trial data, it appears that patients who have shown an improved clinical response have also experienced the greatest weight gain and further, that APD-associated weight gain tends to plateau over time[3,4].

While the mechanism for associated weight gain among APDs has yet to be est
appears to be related to specific receptor antagonism. Further, given the multif
nature of appetite, it is also reasonable to speculate that weight increase results
improved mental state in which patients feel and eat better[5]. The variability i
experience with respect to antipsychotic drug-associated weight gain argues tha
phenomenon is multifactorial, and so far the factors governing this relationship
been clearly defined. The ability to predict vulnerability to APD-associated wei
would be a valuable asset in clinical practice.

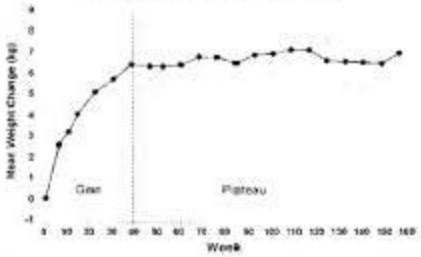
Discussed below are factors influencing body weight change, body weight chan
the largest Zyprexa (olanzapine) clinical trial, HGAJ[6], and comparative data a
conventional and atypical APDs.

FACTORS INFLUENCING WEIGHT CHANGE

Basson, et al [7] analyzed data from two large, international, multi-center, Zyp
trials, HGAJ[6] and HGBG[8], in an attempt to identify factors that influenced
change in patients treated with Zyprexa, haloperidol, and risperidone. Data fro
(N=2335) were compared using repeated measure analysis of variance(ANOV
analyzed eight clinically relevant factors for weight change at Week 6 and at W
These eight factors were clinical response (BPRS), weight prior to Zyprexa tre
[defined by baseline body mass index (BBMI)], appetite disturbance, age, gend
akathisia (Barnes Akathisia Scale[BAS]), and parkinson symptoms (Simpson-A
Scale[SAS]).

Page 4

Figure 2: Mean Change in Weight Over 3 Years
Patients treated with Zyprexa (HGAJ)*



*N=373 at baseline, N=117 at endpoint

The greatest rate of weight gain in this analysis occurred early in the treatment, then slowed down, eventually plateauing at 39 weeks. No data exists to indicate whether a patient will lose weight by switching to another antipsychotic.

LONG TERM ANALYSIS OF BBMI AND DOSE (HGAJ)

As previously stated, BBMI was a factor associated with acute weight change in HGAJ, where patients who were underweight prior to starting a course of antipsychotic treatment gained the most weight. A separate analysis[15] examined the long-term relationship of BBMI to weight change (Figure 3). Patients at baseline were classified as underweight (BBMI <23.6), normal weight (BBMI >23.6 to 27.6), and overweight or obese (BBMI >27.6).

In this analysis, patients at baseline that were overweight or obese had a mean weight change which was significantly less than patients who were normal or underweight ($p<0.001$, both). As indicated in Figure 3, the weight gain of high BBMI patients plateaued at a significantly lower level than low or normal BBMI patients. Of additional importance, 85% of the underweight patients at baseline had an endpoint BMI <27.6 (underweight to normal), potentially explained by underweight Zyprexa-treated patients experiencing a weight restoration due to favorable response to treatment.

Page 6

COMPARATIVE INFORMATION

While antipsychotics are, as a class, associated with weight gain in some patients, weight gain appears to be more common among the atypical antipsychotic agents. For methodological reasons, comparison of drug agents across studies (instead of within the same study) limits the ability to draw conclusions about the relative merits of each drug. Therefore, the best comparative data regarding weight gain among the atypical antipsychotic agents are likely found in direct comparative studies. Discussed below are data from direct comparative studies between Zyprexa and other atypical agents.

Clozapine

The safety and efficacy of Zyprexa were compared to clozapine in a double-blind study in treatment-resistant patients with schizophrenia. Both Zyprexa and clozapine produced significant improvement as measured by ≥20% improvement in PANSS Total score. Additionally, Zyprexa was demonstrated to be at least as effective as clozapine in treatment-resistant schizophrenic patients during 18 weeks of treatment. Safety analysis concluded that no significant difference in weight change was seen between Zyprexa-treated patients (1.8 kg increase) compared to clozapine-treated patients (2.3 kg increase)[17].

Risperidone

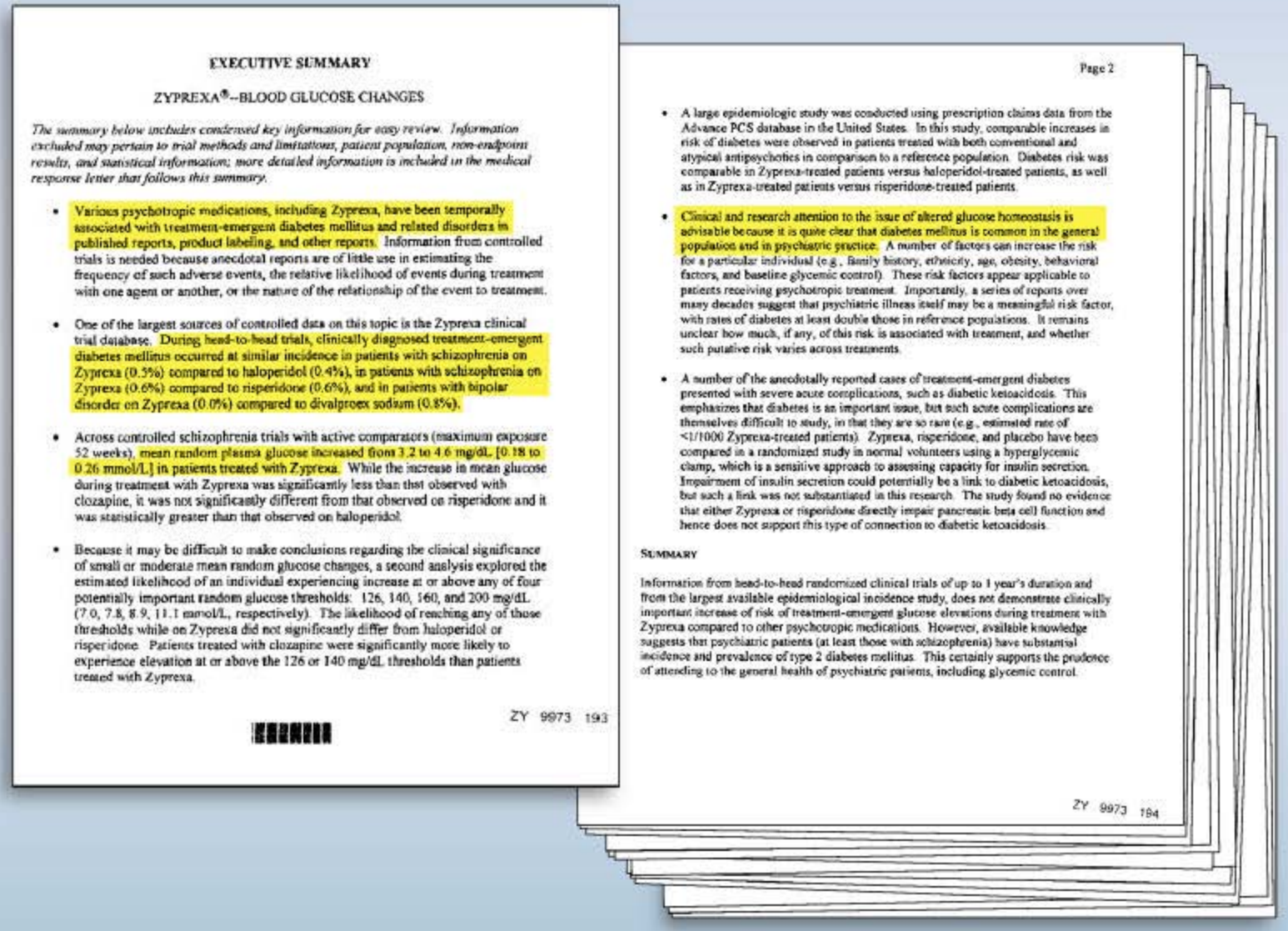
Tran, et al [8] compared the safety and efficacy of Zyprexa and risperidone in 319 patients over 28 weeks. A significantly greater proportion of Zyprexa-treated patients achieved a response rate of at least 40% improvement from baseline in PANSS total score than did the risperidone-treated patients at 28 weeks (Zyprexa 36.8% versus risperidone 26.3%, $p=0.049$). Additionally, Zyprexa-treated patients experienced superior clinical improvement in negative symptoms ($p=0.020$) and depressive symptoms ($p=0.004$).

Analysis of the safety data indicates that both treatment groups experienced statistically significant weight gain from baseline to endpoint ($p<0.001$). Comparison across treatment groups revealed a statistically significantly ($p=0.015$) greater weight gain associated with Zyprexa (4.1 kg) compared with risperidone (2.3 kg). However, the clinical significance of this difference is questionable given the relatively small (1.8 kg) absolute difference over 28 weeks. These data calculations utilized last observation carried forward (LOCF) methodology. This is notable because a higher percentage of Zyprexa-treated patients completed this study, thus allowing for longer drug exposure.

MANAGEMENT OF WEIGHT GAIN ASSOCIATED WITH TREATMENT

A search of the literature indicates that antipsychotic-induced weight gain may be managed by dietary control[1]. There are also cases where antipsychotic induced weight gain appeared to be reversible[18-20]. At the current time, guidelines for the management of

Medical Letter:
Zyprexa – Blood Glucose Changes



EXECUTIVE SUMMARY

ZYPREXA®--BLOOD GLUCOSE CHANGES

The summary below includes condensed key information for easy review. Information excluded may pertain to trial methods and limitations, patient population, non-endpoint results, and statistical information; more detailed information is included in the medical response letter that follows this summary.

- Various psychotropic medications, including Zyprexa, have been temporally associated with treatment-emergent diabetes mellitus and related disorders in published reports, product labelling, and other reports. Information from controlled trials is needed because anecdotal reports are of little use in estimating the frequency of such adverse events, the relative likelihood of events during treatment with one agent or another, or the nature of the relationship of the event to treatment.
- One of the largest sources of controlled data on this topic is the Zyprexa clinical trial database. During head-to-head trials, clinically diagnosed treatment-emergent diabetes mellitus occurred at similar incidence in patients with schizophrenia on Zyprexa (0.3%) compared to haloperidol (0.4%), in patients with schizophrenia on Zyprexa (0.6%) compared to risperidone (0.6%), and in patients with bipolar disorder on Zyprexa (0.0%) compared to divalproex sodium (0.8%).
- Across controlled schizophrenia trials with active comparators (maximum exposure 52 weeks), mean random plasma glucose increased from 3.2 to 4.6 mg/dL [0.18 to 0.26 mmol/L] in patients treated with Zyprexa. While the increase in mean glucose during treatment with Zyprexa was significantly less than that observed with clozapine, it was not significantly different from that observed on risperidone and it was statistically greater than that observed on haloperidol.
- Because it may be difficult to make conclusions regarding the clinical significance of small or moderate mean random glucose changes, a second analysis explored the estimated likelihood of an individual experiencing increase at or above any of four potentially important random glucose thresholds: 126, 140, 160, and 200 mg/dL (7.0, 7.8, 8.9, 11.1 mmol/L, respectively). The likelihood of reaching any of those thresholds while on Zyprexa did not significantly differ from haloperidol or risperidone. Patients treated with clozapine were significantly more likely to experience elevation at or above the 126 or 140 mg/dL thresholds than patients treated with Zyprexa.

ZY 9973 193

- A large epidemiologic study was conducted using prescription claims data from the Advance PCS database in the United States. In this study, comparable increases in risk of diabetes were observed in patients treated with both conventional and atypical antipsychotics in comparison to a reference population. Diabetes risk was comparable in Zyprexa-treated patients versus haloperidol-treated patients, as well as in Zyprexa-treated patients versus risperidone-treated patients.
- Clinical and research attention to the issue of altered glucose homeostasis is advisable because it is quite clear that diabetes mellitus is common in the general population and in psychiatric practice. A number of factors can increase the risk for a particular individual (e.g., family history, ethnicity, age, obesity, behavioral factors, and baseline glycemic control). These risk factors appear applicable to patients receiving psychotropic treatment. Importantly, a series of reports over many decades suggest that psychiatric illness itself may be a meaningful risk factor, with rates of diabetes at least double those in reference populations. It remains unclear how much, if any, of this risk is associated with treatment, and whether such putative risk varies across treatments.
- A number of the anecdotally reported cases of treatment-emergent diabetes presented with severe acute complications, such as diabetic ketoacidosis. This emphasizes that diabetes is an important issue, but such acute complications are themselves difficult to study, in that they are so rare (e.g., estimated rate of <1/1000 Zyprexa-treated patients). Zyprexa, risperidone, and placebo have been compared in a randomized study in normal volunteers using a hyperglycemic clamp, which is a sensitive approach to assessing capacity for insulin secretion. Impairment of insulin secretion could potentially be a link to diabetic ketoacidosis, but such a link was not substantiated in this research. The study found no evidence that either Zyprexa or risperidone directly impair pancreatic beta cell function and hence does not support this type of connection to diabetic ketoacidosis.

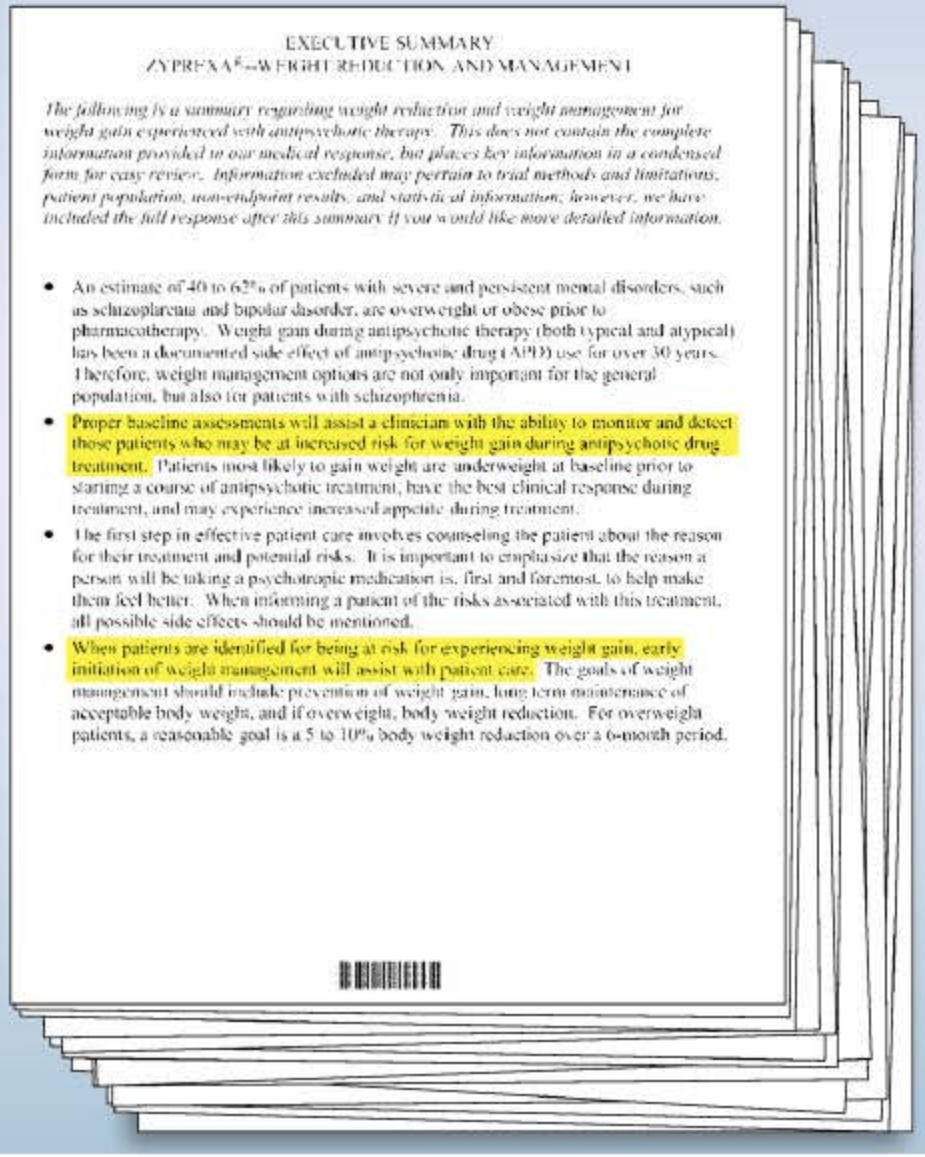
SUMMARY

Information from head-to-head randomized clinical trials of up to 1 year's duration and from the largest available epidemiological incidence study, does not demonstrate clinically important increase of risk of treatment-emergent glucose elevations during treatment with Zyprexa compared to other psychotropic medications. However, available knowledge suggests that psychiatric patients (at least those with schizophrenia) have substantial incidence and prevalence of type 2 diabetes mellitus. This certainly supports the prudence of attending to the general health of psychiatric patients, including glycemic control.

ZY 9973 194

EL 2986

Medical Letter:
Zyprexa – Weight Reduction and Management



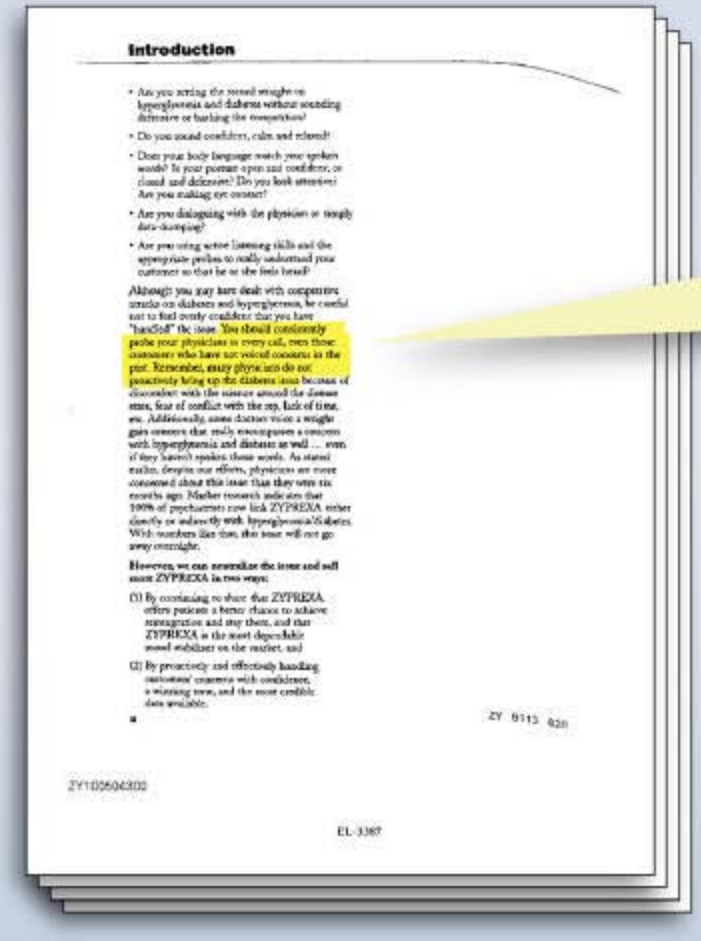
EXECUTIVE SUMMARY
ZYPREXA®—WEIGHT REDUCTION AND MANAGEMENT

The following is a summary regarding weight reduction and weight management for weight gain experienced with antipsychotic therapy. This does not contain the complete information provided to our medical response, but places key information in a condensed form for easy review. Information excluded may pertain to trial methods and limitations, patient population, non-endpoint results, and statistical information; however, we have included the full response after this summary. If you would like more detailed information.

- An estimate of 40 to 62% of patients with severe and persistent mental disorders, such as schizophrenia and bipolar disorder, are overweight or obese prior to pharmacotherapy. Weight gain during antipsychotic therapy (both typical and atypical) has been a documented side effect of antipsychotic drug (APD) use for over 30 years. Therefore, weight management options are not only important for the general population, but also for patients with schizophrenia.
- Proper baseline assessments will assist a clinician with the ability to monitor and detect those patients who may be at increased risk for weight gain during antipsychotic drug treatment. Patients most likely to gain weight are underweight at baseline prior to starting a course of antipsychotic treatment, have the best clinical response during treatment, and may experience increased appetite during treatment.
- The first step in effective patient care involves counseling the patient about the reason for their treatment and potential risks. It is important to emphasize that the reason a person will be taking a psychotropic medication is, first and foremost, to help make them feel better. When informing a patient of the risks associated with this treatment, all possible side effects should be mentioned.
- When patients are identified for being at risk for experiencing weight gain, early initiation of weight management will assist with patient care. The goals of weight management should include prevention of weight gain, long-term maintenance of acceptable body weight, and if overweight, body weight reduction. For overweight patients, a reasonable goal is a 5 to 10% body weight reduction over a 6-month period.

EL 3004

Hyperglycemia/Diabetes Data on Demand Resource Guide (September 2001)



Introduction

- Are you acting the trusted weight on hyperglycemia and diabetes without sounding defensive or bashing the competition?
- Do you sound confident, calm and relaxed?
- Does your body language match your spoken words? Is your posture open and confident, or closed and defensive? Do you look attentive? Are you making eye contact?
- Are you dialoguing with the physician or simply data-dumping?
- Are you using active listening skills and the appropriate probes to really understand your customer so that he or she feels heard?

Although you may have dealt with competitive attacks on diabetes and hyperglycemia, be careful not to feel overly confident that you have "handled" the issue. You should consistently probe your physicians in every call, even those customers who have not voiced concerns in the past. Remember, many physicians do not proactively bring up the diabetes issue because of discomfort with the answer around the disease state, fear of conflict with the rep, lack of time, etc. Additionally, some doctors voice a weight gain concern that really encompasses a concern with hyperglycemia and diabetes as well ... even if they haven't spoken those words. As stated earlier, despite our efforts, physicians are more concerned about this issue than they were six months ago. Market research indicates that 100% of psychiatrists now link ZYPREXA either directly or indirectly with hyperglycemia/diabetes. With numbers like that, this issue will not go away overnight.

However, we can neutralize the issue and sell more ZYPREXA in two ways:

(1) By continuing to share that ZYPREXA offers patients a better chance to achieve remargination and stay there, and that ZYPREXA is the most dependable mood stabilizer on the market, and

(2) By proactively and effectively handling customers' concerns with confidence, a winning tone, and the most credible data available.

ZY 9113 920

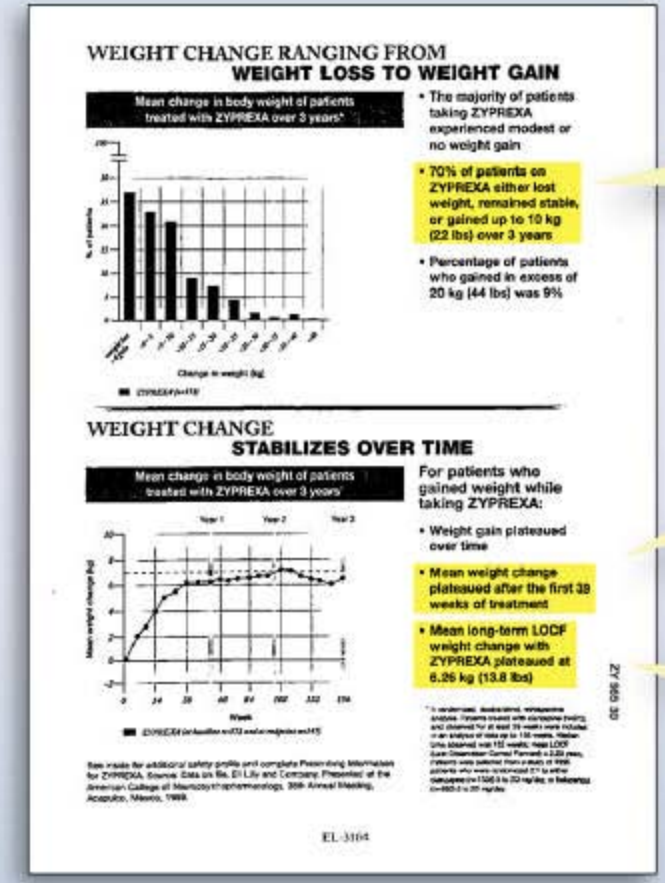
ZY1005043332

EL 3387

You should consistently probe your physicians in every call, even those customers who have not voiced concerns in the past. Remember, many physicians do not proactively bring up the diabetes issue....

EL 3387

Additional Weight Gain Information Provided by Lilly (2000)



WEIGHT CHANGE RANGING FROM
WEIGHT LOSS TO WEIGHT GAIN

Mean change in body weight of patients treated with ZYPREXA over 3 years*

- The majority of patients taking ZYPREXA experienced modest or no weight gain
- 70% of patients on ZYPREXA either lost weight, remained stable, or gained up to 10 kg (22 lbs) over 3 years
- Percentage of patients who gained in excess of 20 kg (44 lbs) was 9%

WEIGHT CHANGE
STABILIZES OVER TIME

Mean change in body weight of patients treated with ZYPREXA over 3 years*

For patients who gained weight while taking ZYPREXA:

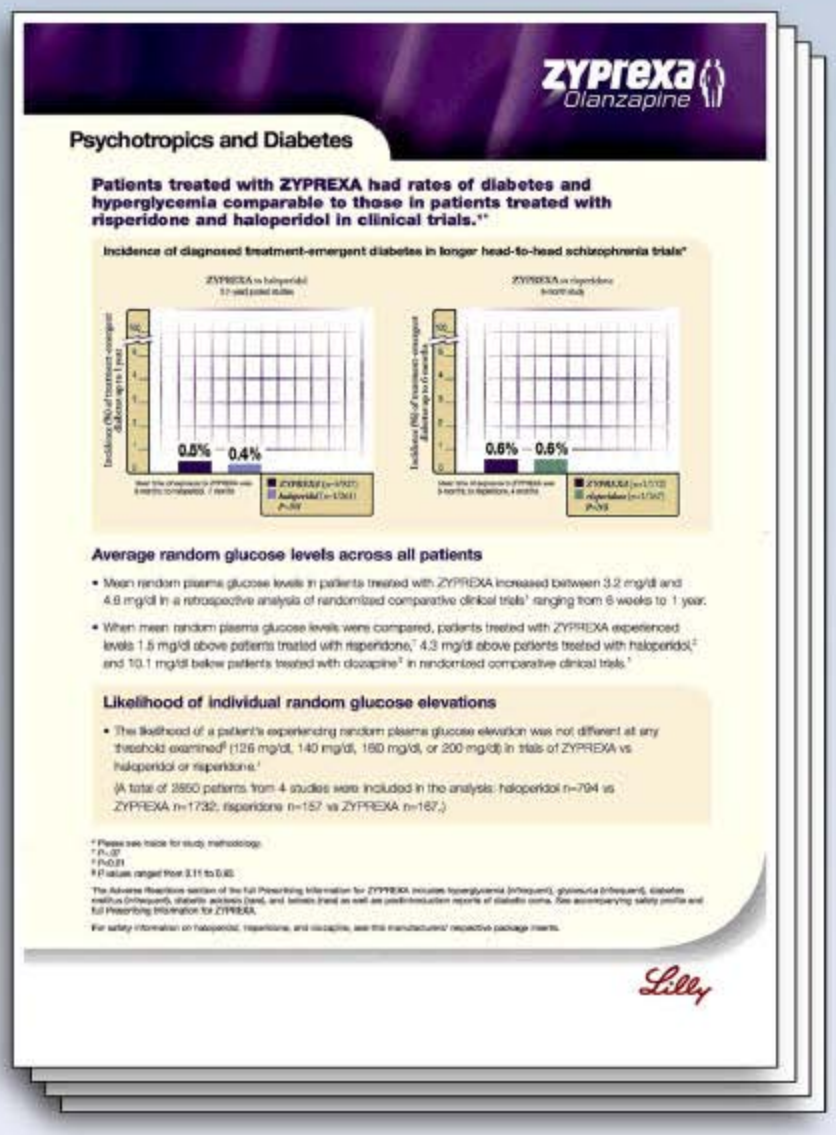
- Weight gain plateaued over time
- Mean weight change plateaued after the first 39 weeks of treatment
- Mean long-term LOCF weight change with ZYPREXA plateaued at 6.26 kg (13.8 lbs)

ZY 669 35

EL-3164

- 70% of patients on ZYPREXA either lost weight, remained stable, or gained up to 10 kg (22 lbs) over 3 years
- Mean weight change plateaued after the first 39 weeks of treatment
- Mean long-term LOCF weight change with ZYPREXA plateaued at 6.26 kg (13.8 lbs)

Hyperglycemia/Diabetes Information Provided by Lilly (February 2001)



ZYPREXA Olanzapine

Psychotropics and Diabetes

Patients treated with ZYPREXA had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone and haloperidol in clinical trials.**

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia trials*

0.5% 0.4%

0.6% 0.6%

Average random glucose levels across all patients

- Mean random plasma glucose levels in patients treated with ZYPREXA increased between 3.2 mg/dl and 4.6 mg/dl in a retrospective analysis of randomized comparative clinical trials† ranging from 6 weeks to 1 year.
- When mean random plasma glucose levels were compared, patients treated with ZYPREXA experienced levels 1.5 mg/dl above patients treated with risperidone,† 4.3 mg/dl above patients treated with haloperidol,‡ and 10.1 mg/dl below patients treated with clozapine§ in randomized comparative clinical trials.†

Likelihood of individual random glucose elevations

- The likelihood of a patient's experiencing random plasma glucose elevation was not different at any threshold examined¶ (126 mg/dl, 140 mg/dl, 160 mg/dl, or 200 mg/dl) in trials of ZYPREXA vs haloperidol or risperidone.†

  (A total of 3850 patients from 4 studies were included in the analysis: haloperidol n=794 vs ZYPREXA n=1732; risperidone n=157 vs ZYPREXA n=167.)

* Please see Inside for study methodology.
† P=.07
‡ P=0.01
¶ P values ranged from 0.11 to 0.49.

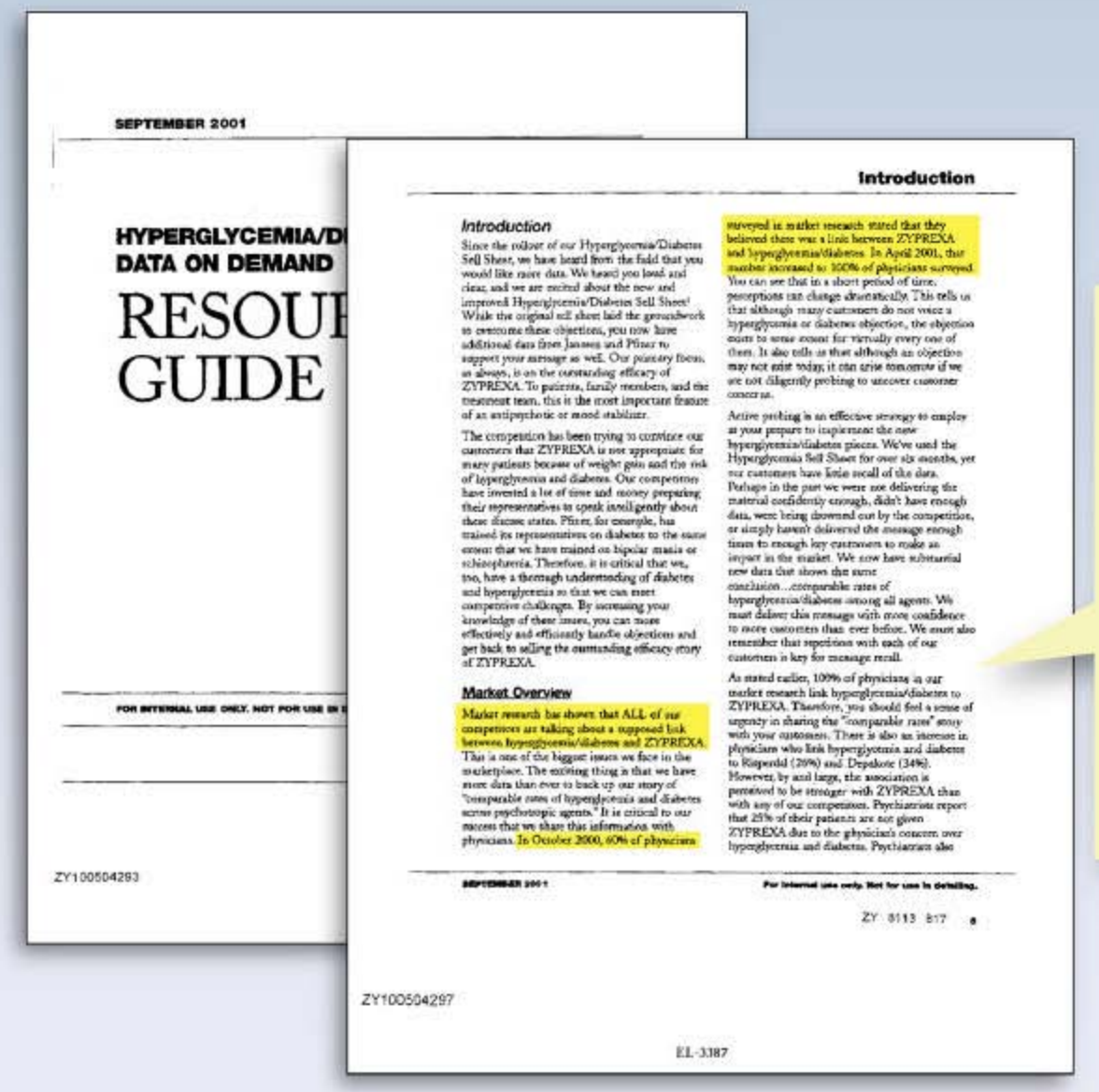
The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma. See accompanying safety profile and full Prescribing Information for ZYPREXA.

For safety information on haloperidol, risperidone, and clozapine, see the manufacturers' respective package inserts.

Lilly

EL 3351

Lilly Market Research



SEPTEMBER 2001

HYPERGLYCEMIA/D
DATA ON DEMAND

RESOU
GUIDE

FOR INTERNAL USE ONLY. NOT FOR USE IN

ZY100504293

Introduction

Introduction

Since the rollout of our Hyperglycemia/Diabetes Sell Sheet, we have heard from the field that you would like more data. We heard you loud and clear, and we are excited about the new and improved Hyperglycemia/Diabetes Sell Sheet! While the original sell sheet laid the groundwork to overcome these objections, you now have additional data from Janssen and Pfizer to support your message as well. Our primary focus, as always, is on the outstanding efficacy of ZYPREXA. To patients, family members, and the treatment team, this is the most important feature of an antipsychotic or mood stabilizer.

The competition has been trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain and the risk of hyperglycemia and diabetes. Our competitors have invested a lot of time and money preparing their representatives to speak intelligently about these disease states. Pfizer, for example, has trained its representatives on diabetes to the same extent that we have trained on bipolar mania or schizophrenia. Therefore, it is critical that we, too, have a thorough understanding of diabetes and hyperglycemia so that we can meet competitive challenges. By increasing your knowledge of these issues, you can more effectively and efficiently handle objections and get back to selling the outstanding efficacy story of ZYPREXA.

Market Overview

Market research has shown that ALL of our competitors are talking about a supposed link between hyperglycemia/diabetes and ZYPREXA. This is one of the biggest issues we face in the marketplace. The exciting thing is that we have more data than ever to back up our story of "comparable rates of hyperglycemia and diabetes across psychotropic agents." It is critical to our success that we share this information with physicians. In October 2000, 60% of physicians surveyed in market research stated that they believed there was a link between ZYPREXA and hyperglycemia/diabetes. In April 2001, that number increased to 100% of physicians surveyed. You can see that in a short period of time, perceptions can change dramatically. This tells us that although many customers do not voice a hyperglycemia or diabetes objection, the objection seems to arise enough for virtually every one of them. It also tells us that although an objection may not exist today, it can arise tomorrow if we are not diligently probing to uncover customer concerns.

Active probing is an effective strategy to employ as your prepare to implement the new hyperglycemia/diabetes pieces. We've used the Hyperglycemia Sell Sheet for over six months, yet our customers have little recall of the data. Perhaps in the past we were not delivering the material confidently enough, didn't have enough data, were being drowned out by the competition, or simply haven't delivered the message enough times to enough key customers to make an impact in the market. We now have substantial new data that shows the same conclusion…comparable rates of hyperglycemia/diabetes among all agents. We must deliver this message with more confidence to more customers than ever before. We must also remember that repetition with each of our customers is key for message recall.

As stated earlier, 100% of physicians in our market research link hyperglycemia/diabetes to ZYPREXA. Therefore, you should feel a sense of urgency in sharing the "comparable rates" story with your customers. There is also an interest in physicians who link hyperglycemia and diabetes to Risperdal (29%) and Depakote (34%). However, by and large, the association is perceived to be stronger with ZYPREXA than with any of our competitors. Psychiatrists report that 25% of their patients are not given ZYPREXA due to the physician's concern over hyperglycemia and diabetes. Psychiatrists also

SEPTEMBER 2001 — For internal use only. Not for use in detailing.

ZY 0113 817 6

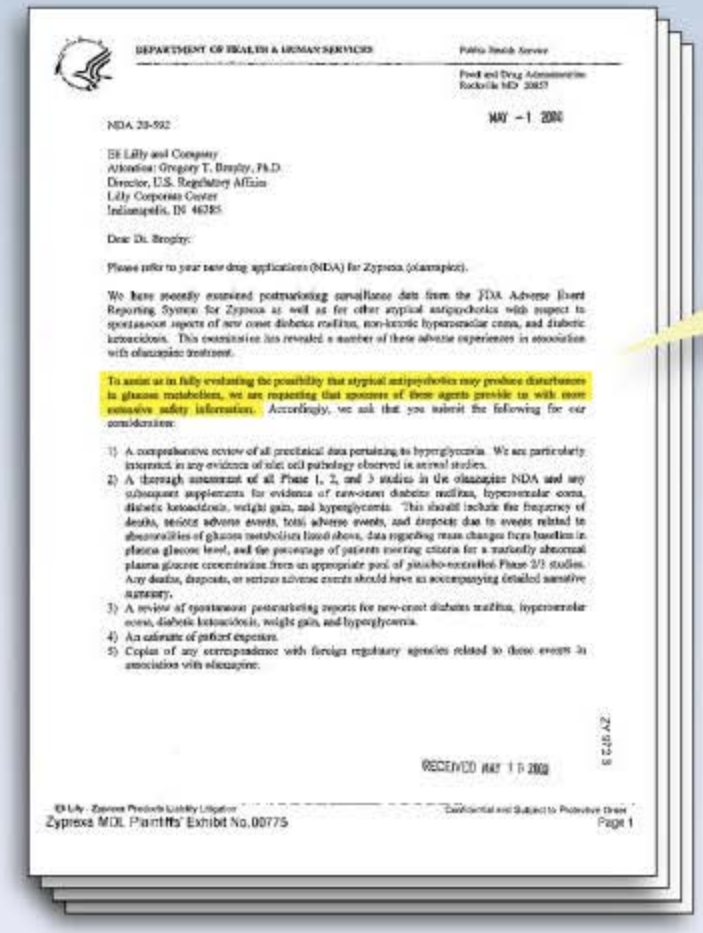
ZY100504297

EL-3387

In October 2000, 60% of physicians surveyed in market research stated that they believed there was a link between ZYPREXA and hyperglycemia/diabetes. In April 2001, that number increased to 100% of physicians surveyed.

EL 3387

May 2000 FDA Letter



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-592

MAY – 1 2000

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) for Zyprexa (olanzapine).

We have recently examined postmarketing surveillance data from the FDA Adverse Event Reporting System for Zyprexa as well as for other atypical antipsychotics with respect to spontaneous reports of new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis. This examination has revealed a number of these adverse experiences in association with olanzapine treatment.

To assist us in fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose metabolism, we are requesting that sponsors of these agents provide us with more extensive safety information. Accordingly, we ask that you submit the following for our consideration:

1) A comprehensive review of all preclinical data pertaining to hyperglycemia. We are particularly interested in any evidence of islet cell pathology observed in animal studies.
2) A thorough assessment of all Phase 1, 2, and 3 studies in the olanzapine NDA and any subsequent supplements for evidence of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia. This should include the frequency of deaths, serious adverse events, total adverse events, and dropouts due to events related to abnormalities of glucose metabolism listed above, data regarding mean changes from baseline in plasma glucose level, and the percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration from an appropriate pool of placebo-controlled Phase 2/3 studies. Any deaths, dropouts, or serious adverse events should have an accompanying detailed narrative summary.
3) A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia.
4) An estimate of patient exposure.
5) Copies of any correspondence with foreign regulatory agencies related to these events in association with olanzapine.

RECEIVED MAY 1 5 2000

Eli Lilly - Zyprexa Products Liability Litigation

Confidential and Subject to Protective Order

Zyprexa MDL Plaintiffs' Exhibit No.00775

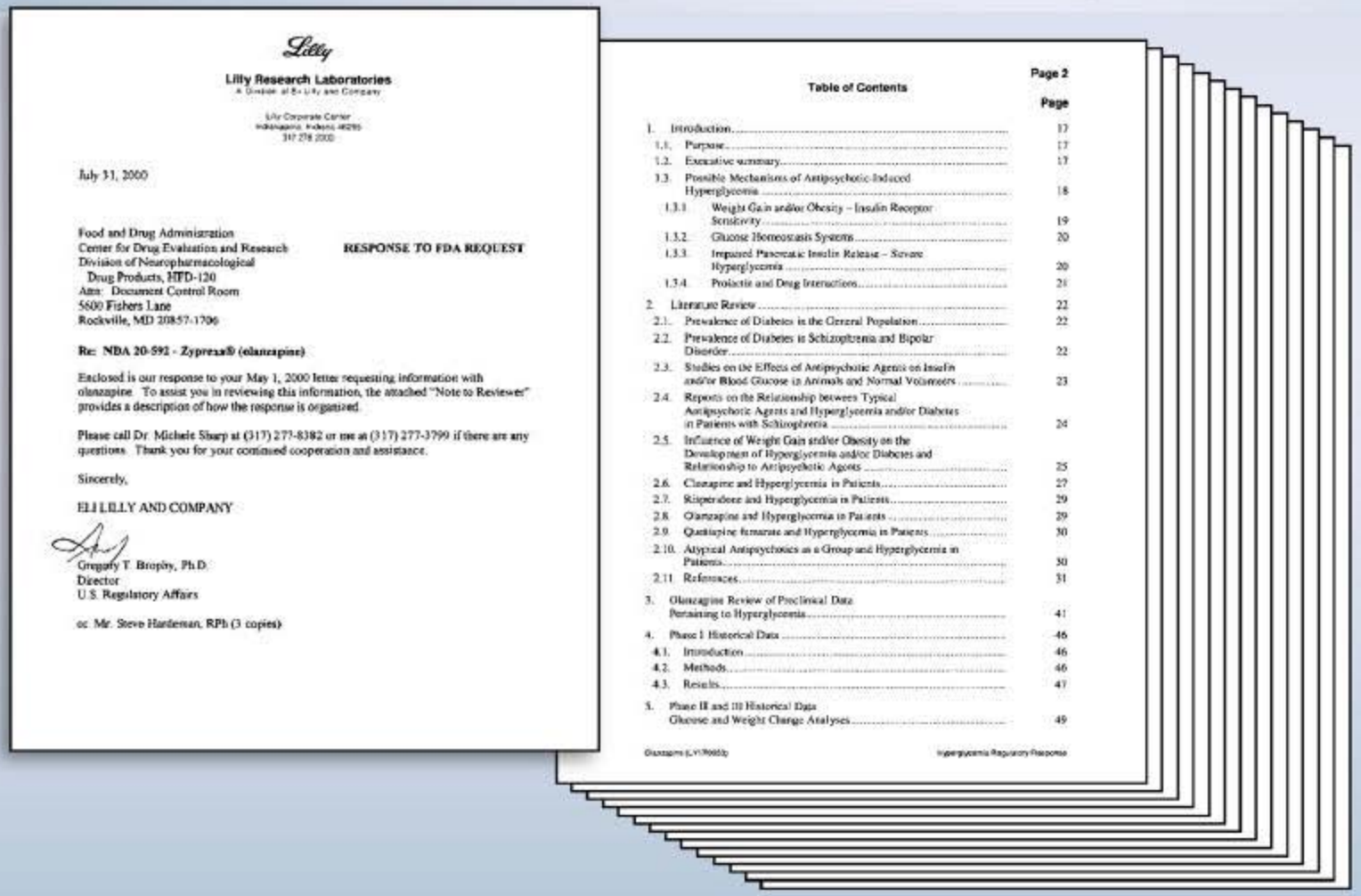
Page 1

To assist us in fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose metabolism, we are requesting that sponsors of these agents provide us with more extensive safety information.

PX 0775

July 31, 2000

First major submission on hyperglycemia and diabetes after more than 4 million exposures



Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317 276 2000

July 31, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

RESPONSE TO FDA REQUEST

Re: NDA 20-592 - Zyprexa® (olanzapine)

Enclosed is our response to your May 1, 2000 letter requesting information with olanzapine. To assist you in reviewing this information, the attached "Note to Reviewer" provides a description of how the response is organized.

Please call Dr. Michele Sharp at (317) 277-8382 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

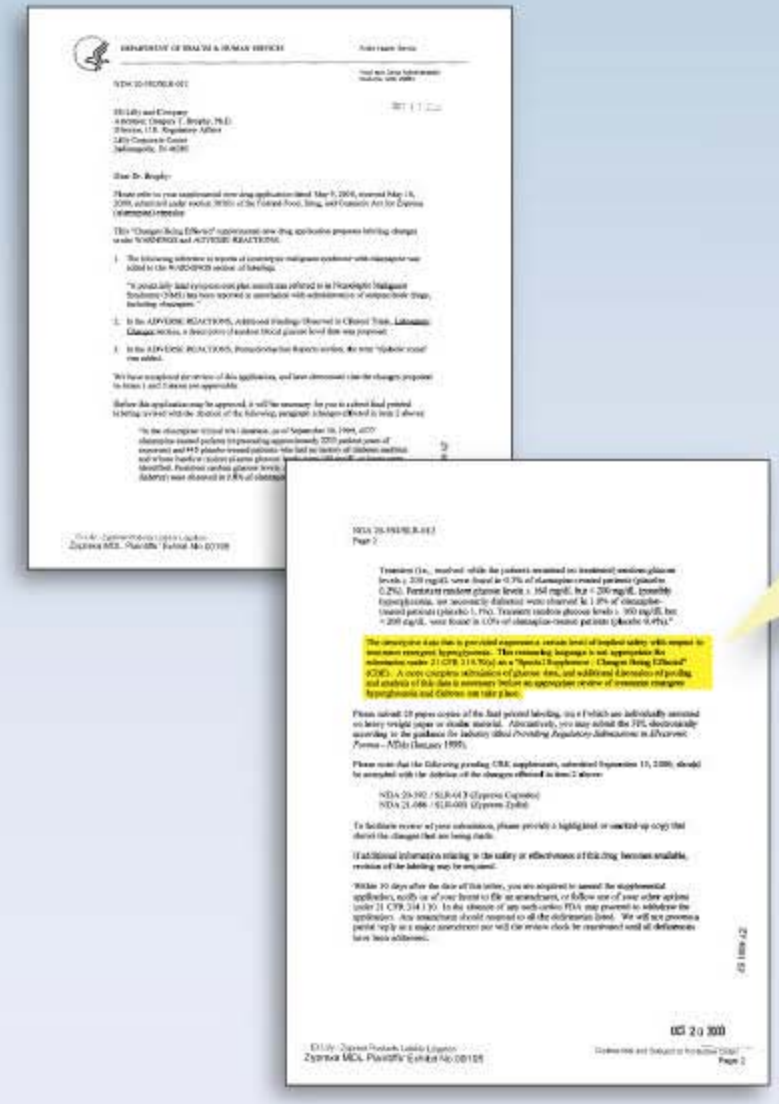
cc: Mr. Steve Hardeman, RPh (3 copies)

Table of Contents

Page 2

EL 2043

October 2000 FDA Letter



The descriptive data that is provided expresses a certain level of implied safety with respect to treatment emergent hyperglycemia. This reassuring language is not appropriate for submission under 21 CFR 314.70(c) as a "Special Supplement – Changes Being Effected" (CBE). A more complete submission of glucose data, and additional discussion of pooling and analysis of this data is necessary before an appropriate review of treatment emergent hyperglycemia and diabetes can take place.

PX00195

May 21, 2001

Clinical trial analysis and two epidemiological studies regarding diabetes

May 21, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

RESPONSE TO FDA REQUEST

Re: NDA 20-592 – Zyprexa (olanzapine)

Enclosed is additional information regarding our initial response (submitted on July 31, 2000) to your May 1, 2000 letter pertaining to hyperglycemia. The attached "Note to Reviewer" provides a description of the additional data and analyses provided in this submission in order to assist your review.

Please call Dr. Michele Sharp at (317) 277-8582 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Mr. Steve Hardeman, RPh (12 desk copies)

Answers That Matter.

State of Alaska v. Eli Lilly Co. Confidential - Subject to Protective Order
EL 2038

ZYAK-AG2005369

Attachment 1

Diabetes Mellitus and Antipsychotic Treatment
in the United States
A Pharmacoepidemiological Study Utilizing the
AdvancePCS Prescription Claim Database

5/21/2001

State of Alaska v. Eli Lilly Co. Confidential - Subject to Protective Order
EL-2038

ZYAK-AG2005369

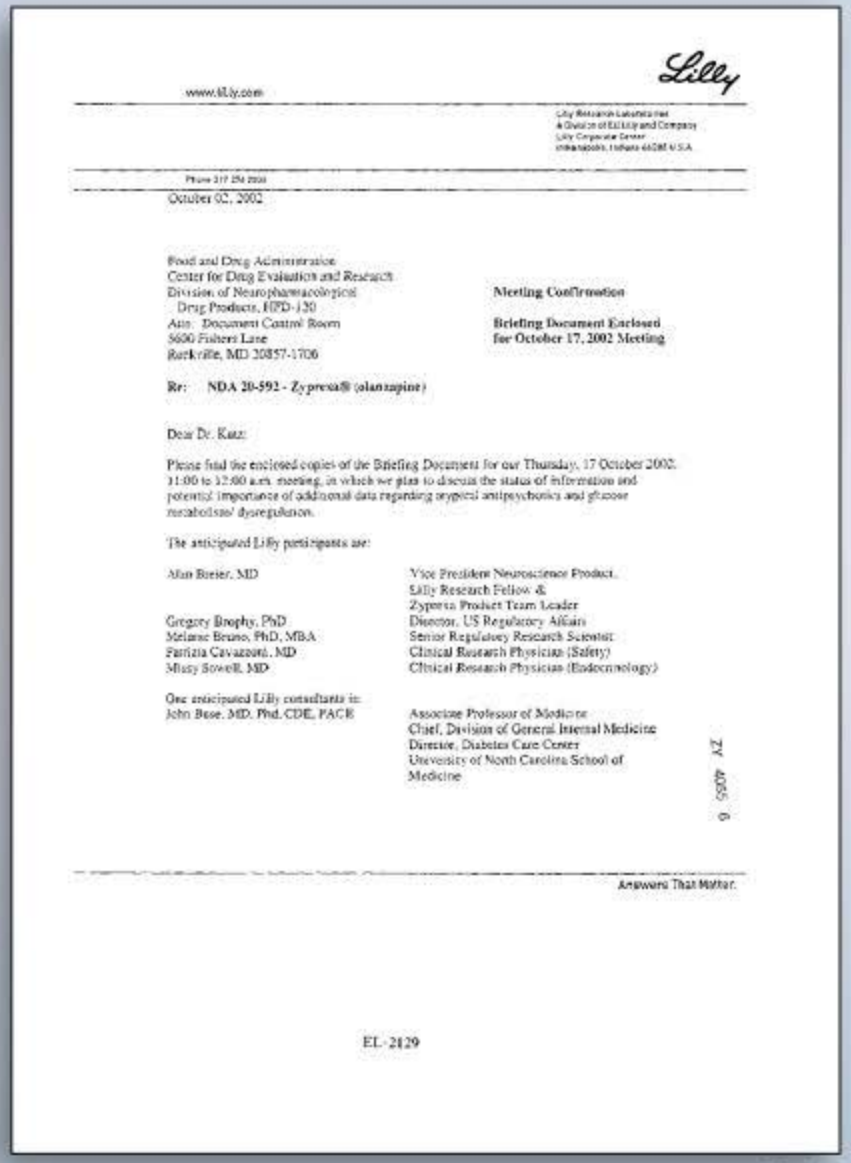
ZYAK-AG2005371

ZYAK-AG2005736

EL 2038

October 2, 2002

Briefing document reviewing literature, new Lilly studies, and spontaneous adverse events after 9 million exposures



www.lilly.com

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

October 02, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-130
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

Meeting Confirmation

Briefing Document Enclosed for October 17, 2002 Meeting

Re: NDA 20-592 - Zyprexa® (olanzapine)

Dear Dr. Katz:

Please find the enclosed copies of the Briefing Document for our Thursday, 17 October 2002, 11:00 to 12:00 a.m. meeting, in which we plan to discuss the status of information and potential importance of additional data regarding atypical antipsychotics and glucose metabolism/ dysregulation.

The anticipated Lilly participants are:

Alan Breier, MD	Vice President Neuroscience Product, Lilly Research Fellow, & Zyprexa Product Team Leader
Gregory Brophy, PhD	Director, US Regulatory Affairs
Melanie Bruno, PhD, MBA	Senior Regulatory Research Scientist
Fariizia Cavazzoni, MD	Clinical Research Physician (Safety)
Misty Sowell, MD	Clinical Research Physician (Endocrinology)

One anticipated Lilly consultants is:

John Buse, MD, Phd, CDE, FACE	Associate Professor of Medicine Chief, Division of General Internal Medicine Director, Diabetes Care Center University of North Carolina School of Medicine

ZY 4055 6

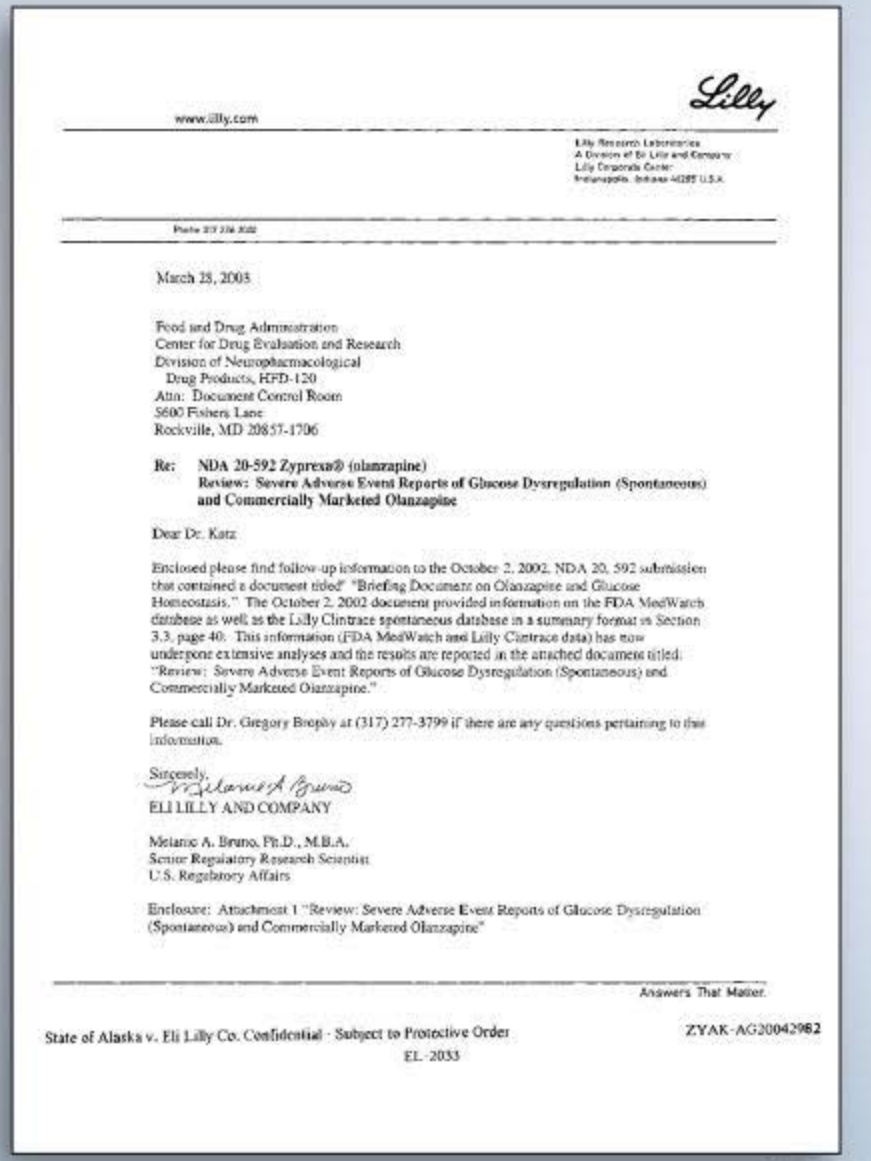
Answers That Matter.

EL-2129

EL 2129

March 28, 2003

Review of severe adverse event reports of glucose dysregulation and commercially marketed olanzapine after 9 million exposures



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Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

March 28, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-592 Zyprexa® (olanzapine)
Review: Severe Adverse Event Reports of Glucose Dysregulation (Spontaneous) and Commercially Marketed Olanzapine

Dear Dr. Katz

Enclosed please find follow-up information to the October 2, 2002, NDA 20, 592 submission that contained a document titled" "Briefing Document on Olanzapine and Glucose Homeostasis." The October 2, 2002 document provided information on the FDA MedWatch database as well as the Lilly Clintrace spontaneous database in a summary format in Section 3.3, page 40. This information (FDA MedWatch and Lilly Clintrace data) has now undergone extensive analyses and the results are reported in the attached document titled: "Review: Severe Adverse Event Reports of Glucose Dysregulation (Spontaneous) and Commercially Marketed Olanzapine."

Please call Dr. Gregory Brophy at (317) 277-3799 if there are any questions pertaining to this information.

Sincerely,

ELI LILLY AND COMPANY

Melanie A. Bruno, Ph.D., M.B.A.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosure: Attachment 1 "Review: Severe Adverse Event Reports of Glucose Dysregulation (Spontaneous) and Commercially Marketed Olanzapine"

Answers That Matter.

State of Alaska v. Eli Lilly Co. Confidential - Subject to Protective Order

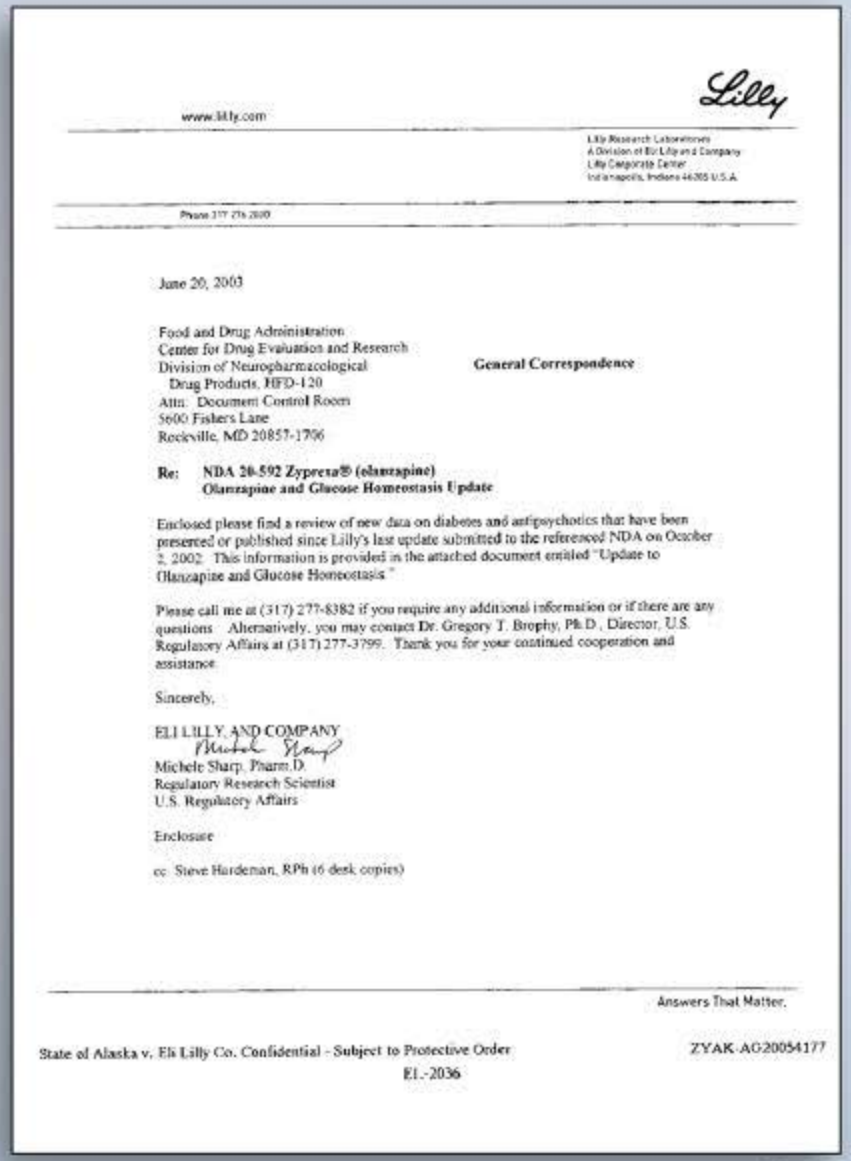
ZYAK-AG20042982

EL-2033

EL 2033

June 20, 2003

Submission of new data and literature on diabetes and antipsychotics



Lilly

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Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

June 20, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

General Correspondence

Re: NDA 20-592 Zyprexa® (olanzapine)
Olanzapine and Glucose Homeostasis Update

Enclosed please find a review of new data on diabetes and antipsychotics that have been presented or published since Lilly's last update submitted to the referenced NDA on October 2, 2002. This information is provided in the attached document entitled "Update to Olanzapine and Glucose Homeostasis."

Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Michele Sharp, Pharm.D.
Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosure

cc: Steve Hardeman, RPh (6 desk copies)

Answers That Matter.

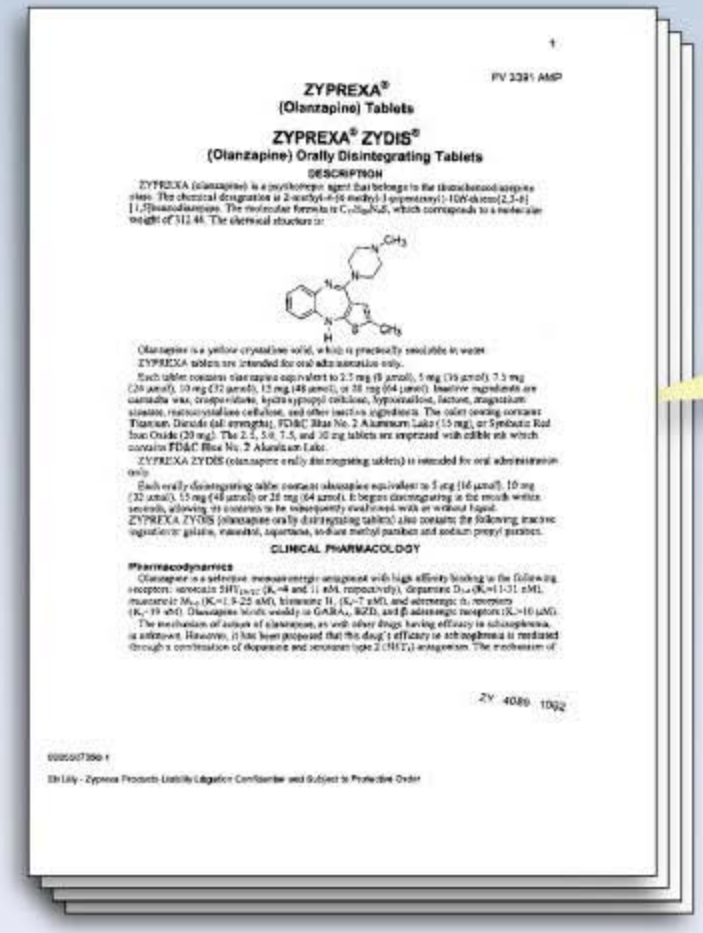
State of Alaska v. Eli Lilly Co. Confidential - Subject to Protective Order

ZYAK-AG20054177

EL-2036

EL 2036

2003 Label: Class Warning



ZYPREXA®
(Olanzapine) Tablets

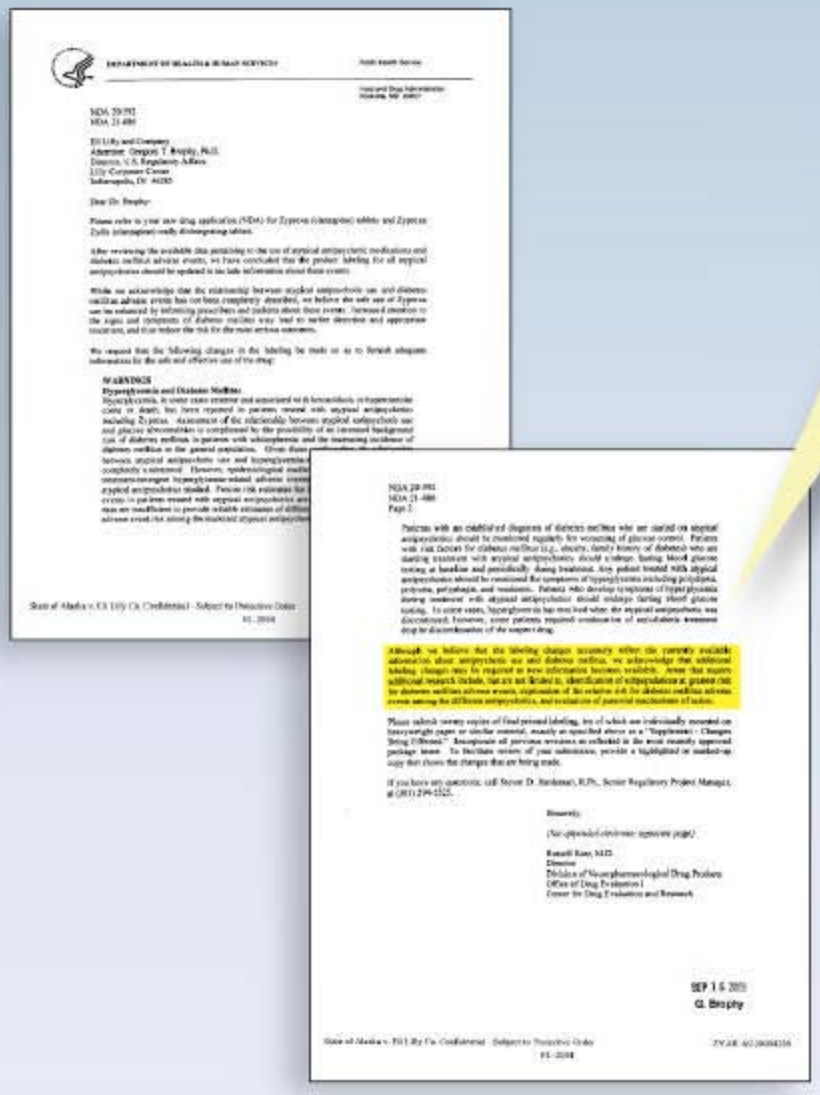
ZYPREXA® ZYDIS®
(Olanzapine) Orally Disintegrating Tablets

DESCRIPTION

CLINICAL PHARMACOLOGY

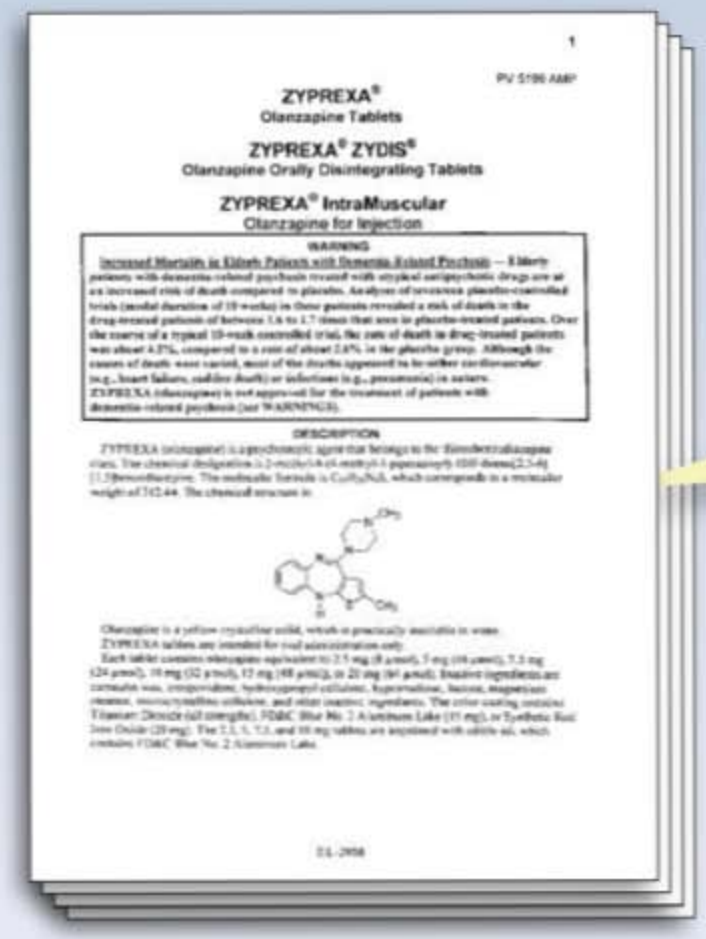
- Increased risk of diabetes mellitus in schizophrenia
- Epidemiological studies suggest an increased risk of hyperglycemia-related adverse events in patients treated with the atypical antipsychotics
- Data is insufficient to provide reliable estimates of differences in risk
- Monitoring recommendations
- "The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood"

September 2003 Letter From FDA



Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

2007 Label



ZYPREXA®
Olanzapine Tablets

ZYPREXA® ZYDIS®
Olanzapine Orally Disintegrating Tablets

ZYPREXA® IntraMuscular
Olanzapine for Injection

WARNING

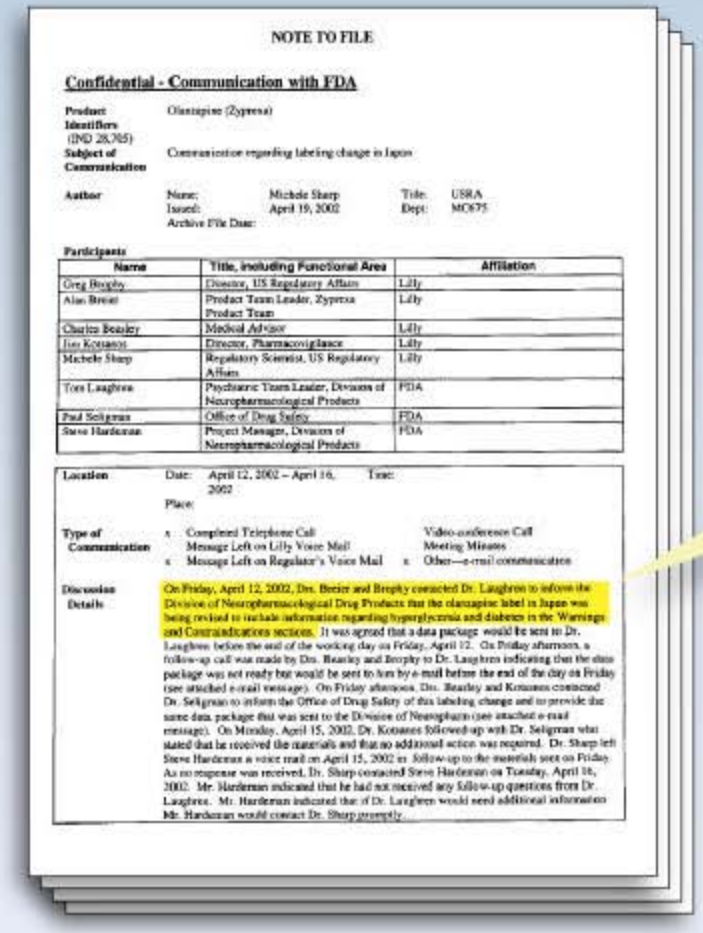
DESCRIPTION

EL-2958

- Abnormal or borderline glucose levels at baseline: important risk factor for further glucose increase.
- While risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum; olanzapine appears to have a greater association than some other atypical antipsychotics.
- Significantly greater mean increases in total cholesterol, LDL, and triglycerides were observed in Zyprexa-treated patients compared with placebo-treated patients.
- Labeling provides information on magnitude and distribution of weight gain over 2 years.
- Labeling provides information on glucose, weight gain, and lipids from studies of Zyprexa for adolescent patients.

EL 2958

Note to File re Japan Label Change



NOTE TO FILE

Confidential - Communication with FDA

Product Identifiers (IND 28,705): Olanzapine (Zyprexa)

Subject of Communication: Communication regarding labeling change in Japan

Author: Name: Michele Sharp; Title: USRA; Issued: April 19, 2002; Dept: MC875; Archive File Date:

Participants

Name	Title, including Functional Area	Affiliation
Greg Brophy	Director, US Regulatory Affairs	Lilly
Alan Breier	Product Team Leader, Zyprexa Product Team	Lilly
Charles Beasley	Medical Advisor	Lilly
Jim Kotsanos	Director, Pharmacovigilance	Lilly
Michele Sharp	Regulatory Scientist, US Regulatory Affairs	Lilly
Tom Laughren	Psychiatric Team Leader, Division of Neuropharmacological Products	FDA
Paul Seligman	Office of Drug Safety	FDA
Steve Hardeman	Project Manager, Division of Neuropharmacological Products	FDA

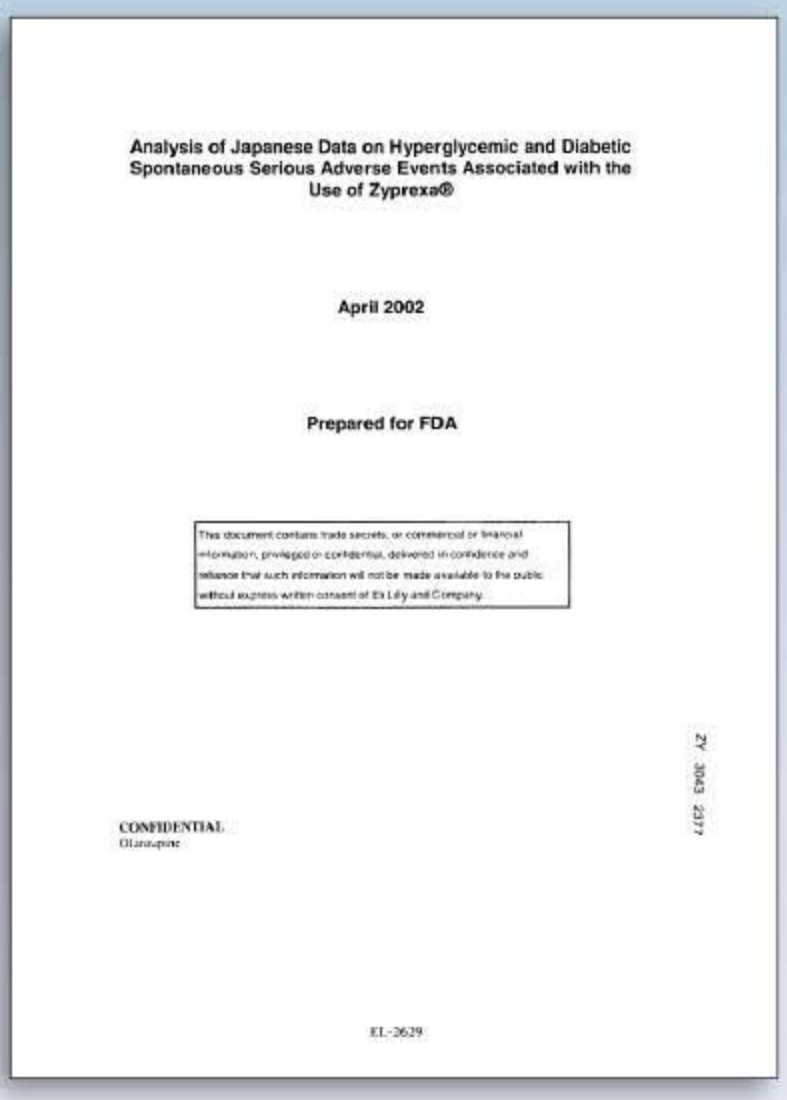
Location: Date: April 12, 2002 – April 16, 2002; Time:; Place:

Type of Communication:
- x Completed Telephone Call
- Message Left on Lilly Voice Mail
- x Message Left on Regulator's Voice Mail
- Video-conference Call
- Meeting Minutes
- x Other—e-mail communication

Discussion Details: On Friday, April 12, 2002, Drs. Breier and Brophy contacted Dr. Laughren to inform the Division of Neuropharmacological Drug Products that the olanzapine label in Japan was being revised to include information regarding hyperglycemia and diabetes in the Warnings and Contraindications sections. It was agreed that a data package would be sent to Dr. Laughren before the end of the working day on Friday, April 12. On Friday afternoon, a follow-up call was made by Drs. Beasley and Brophy to Dr. Laughren indicating that the data package was not ready but would be sent to him by e-mail before the end of the day on Friday (see attached e-mail message). On Friday afternoon, Drs. Beasley and Kotsanos contacted Dr. Seligman to inform the Office of Drug Safety of this labeling change and to provide the same data package that was sent to the Division of Neuropharm (see attached e-mail message). On Monday, April 15, 2002, Dr. Kotsanos followed-up with Dr. Seligman who stated that he received the materials and that no additional action was required. Dr. Sharp left Steve Hardeman a voice mail on April 15, 2002 re: follow-up to the materials sent on Friday. As no response was received, Dr. Sharp contacted Steve Hardeman on Tuesday, April 16, 2002. Mr. Hardeman indicated that he had not received any follow-up questions from Dr. Laughren. Mr. Hardeman indicated that if Dr. Laughren would need additional information Mr. Hardeman would contact Dr. Sharp promptly.

On Friday, April 12, 2002, Drs. Breier and Brophy contacted Dr. Laughren to inform the Division of Neuropharmacological Drug Products that the olanzapine label in Japan was being revised to include information regarding hyperglycemia and diabetes in the Warnings and Contraindications sections.

Submission to FDA re Japan



Analysis of Japanese Data on Hyperglycemic and Diabetic Spontaneous Serious Adverse Events Associated with the Use of Zyprexa®

April 2002

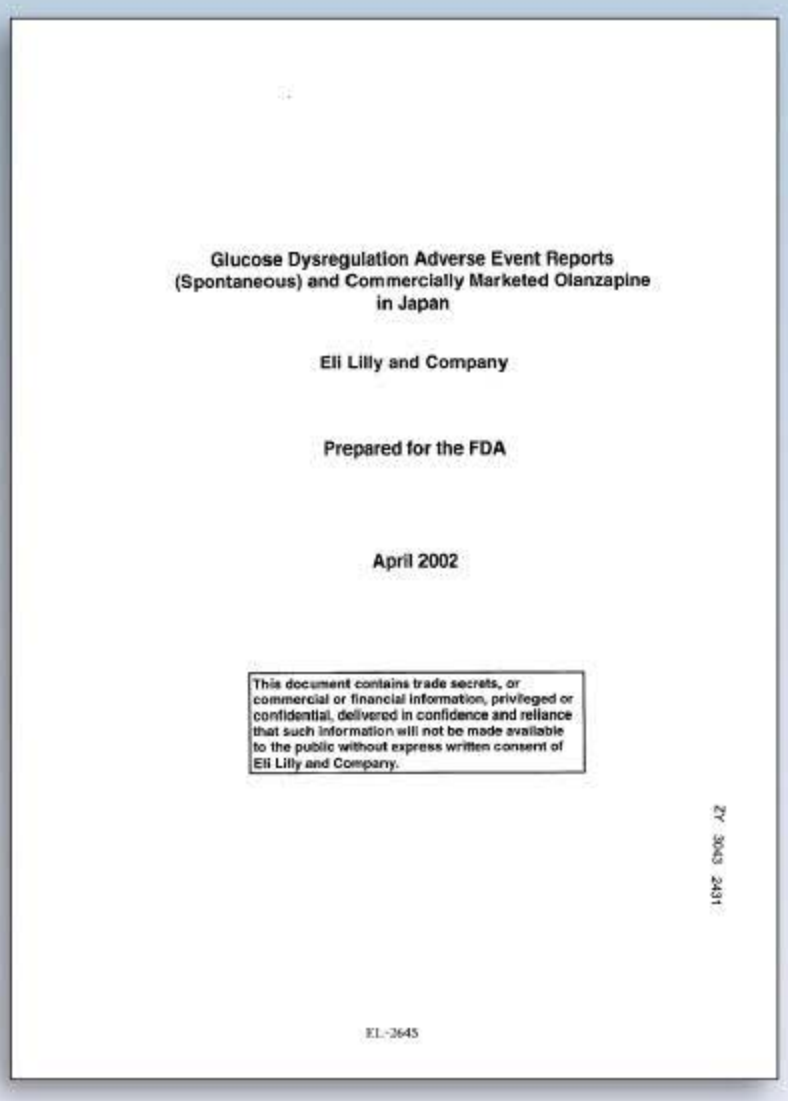
Prepared for FDA

This document contains trade secrets, or commercial or financial information, privileged or confidential, delivered in confidence and reliance that such information will not be made available to the public without express written consent of Eli Lilly and Company.

ZY 3043 2377

CONFIDENTIAL
Olanzapine

EL-2629



Glucose Dysregulation Adverse Event Reports (Spontaneous) and Commercially Marketed Olanzapine in Japan

Eli Lilly and Company

Prepared for the FDA

April 2002

This document contains trade secrets, or commercial or financial information, privileged or confidential, delivered in confidence and reliance that such information will not be made available to the public without express written consent of Eli Lilly and Company.

ZY 3043 2431

EL-2645

EL 2629, EL 2645

FDA Response to Consensus Statement

Letters

References

1. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes (Consensus Statement). Diabetes Care 27: 596–601, 2004
2. Marder SR, Essock SM, Miller AL, Buchanan RW, Davis JM, Kane JM, Lieberman J, Schooler NR. The Mount Sinai Conference on the pharmacotherapy of schizophrenia. Schizophr Bull 29:5–16, 2002
3. Castner L, Jaffe A. Relationship of atypical antipsychotics with development of diabetes mellitus. Ann Pharmacother 37: 1049–1057, 2003
4. Roach J. FDA to require diabetes warning on antipsychotics. Psychiatr News 38(20): 1, 2003
5. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 60: 553–564, 2003
6. Tollefson GD, Goldstein RS, Vollerka J, Conboy P, Heparian M, Sharman B, Lindenmayer JP, Carrome L, McEvoy J, Kanz M, Chafos M, Cooper TB, Horowitz TS, Lieberman JA. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 159:1018–1028, 2002
7. Conboy P, Vollerka J, Sharman B, Lindenmayer JP, Carrome L, McEvoy J, Cooper TB, Chafos M, Lieberman J. Antipsychotic-induced weight gain and therapeutic response: a differential assessment. J Clin Psychopharmacol 23:244–251, 2003
8. Carrome L. Efficacy should drive atypical antipsychotic treatment. Br Med J 326: 183–184, 2003

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to consensus statement

We of course welcome the fact that the issue of obesity and diabetes in the management of psychosis is taken seriously by the disciplines represented in this conference (1). However, as clinical psychiatrists we are concerned that some of the reasons stated may give an unnecessarily misleading message.

We are far from sure, for example, that the evidence supports the view that there is so much disparity in the incidence of obesity and diabetes among first- presumptive consensus panel have the force of law in the wider professional community, not to mention the persons

2088

Letters

these two drugs have not been included in epidemiological studies, this conclusion is solely based on data from clinical trials that did not reveal the risk of treatment-emergent hyperglycemia and diabetes. We must point out that the clinical trial data have not provided strong evidence of a diabetes risk for any of the SGAs. It is not clear whether this is due to the timing of glucose measurements (random in most cases), the low absolute frequency for diabetes events, the short duration of many of the trials, or other factors. Therefore, the DNDP does not consider the absence of a signal in clinical trial data to rule out the risk of diabetes with SGAs.

Based on a review of epidemiological studies, the ADA concluded that there is an increased risk of diabetes with olanzapine and clozapine and discrepant results with quetiapine and risperidone. The ADA correctly identifies many of the limitations of these epidemiological studies, including "their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. . . relatively short periods of study, . . . failure to control for a possible treatment sequence bias in 'switchover' studies, and . . . not always using clinically equivalent dosages of the medications." The DNDP believes that although these studies support an increased risk of treatment-emergent hyperglycemia or diabetes, compared with patients treated with older antipsychotic drugs, the limitations of these studies preclude firm conclusions about the relative risk for diabetes among the studied SGAs.

The ADA asserts that "weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., . . . diabetes . . ." The ADA correctly points out that SGAs have different weight gain liabilities. Although weight gain may be a factor in explaining the increased diabetes risk for SGAs, DNDP is not aware of evidence proving that the treatment-emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. Although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and epidemiological evidence has not shown a direct link between these treatment-emergent side effects. A substantial proportion (~25%) of adverse event reports submitted to the U.S. Food and Drug Administration do not mention weight gain as part of the presentation of SGA-associated hyperglycemia or diabetes.

Although the DNDP agrees with the ADA's recommendation to reexamine patients treated with SGAs for evidence of diabetes, we do not believe that the available evidence allows the ranking of diabetes risk for these drugs at this time. We agree with the ADA that additional studies are needed to clarify many of the issues surrounding the diabetes-SGA risk relationship. In the meantime, DNDP recommends that clinicians remain vigilant in monitoring all patients treated with SGAs to assure their safe use.

Gerard Boehm, MD, MPH
Judith A. Racoosin, MD, MPH
Thomas P. Laughren, MD
Russell Katz, MD

From the Division of Neuropharmacological Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland.

Address correspondence to Dr. Judith A. Racoosin, 5600 Fishers Ln., HFD-123, Rockville, MD 20857. E-mail: racoosinj@cder.fda.gov.

References

1. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes (Consensus Statement). Diabetes Care 27: 596–601, 2004

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to Holt, Citrome and Volavka, Isaac and Isaac, and Boehm et al.

We appreciate the opportunity to comment on the letters that have been received in response to our recent consensus statement on antipsychotic drugs and obesity and diabetes.

Before addressing the specific issues raised in each of these letters, I think it is important to note why the American Diabetes Association (ADA) and other organizations produce consensus statements (1). As stated in our clinical practice recommendations, "the need for a consensus statement arises when clinicians or scientists desire guidance on a subject for which there is a relative deficiency of comprehensive evidence that might otherwise allow for a more definitive statement to be made." Therefore, it should be noted that such statements represent the expert opinion of the panel based on the presentations they heard, the literature they reviewed, and the considerable discussion among panel members while writing the statement. If there was a reasonable number of randomized control trials on the subject, there would be no need for a consensus statement, but rather the associations would issue an official "Position Statement" or clinical guideline. Thus, a consensus statement can be viewed as an expert recommendation that often precedes more definitive recommendations issued when sufficient additional data become available. These may or may not be different from those in the initial consensus statement.

The letter from Holt (2) comments that he was a member of another group that reviewed the evidence surrounding this issue and reached conclusions "that differed in some respects" from those of the ADA consensus panel. Their recommendations are due to be published soon. We are, of course, delighted that another group has deliberated seriously on this important, clinical question and look forward to seeing their conclusions and recommendations. We hope that much needed data come to bear on this issue in the near term. We also support Holt and each of the other correspondents in pointing out that antipsychotic medications are essential for people with schizophrenia and that their differential effectiveness is very important. We purposefully used the word "consider" throughout our statement to suggest that the advice we gave with regard to avoiding undesirable side effects should be one of many factors in deciding which medication to use. Such risk-benefit considerations are essential.

Citrome and Volavka (3) comment that "the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes." We disagree with this statement and believe that the

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...DNDP is not aware of evidence proving that the treatment-emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. Although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and epidemiological evidence has not shown a direct link between these treatment-emergent side effects.

* * *

Gerard Boehm, MD, MPH
Judith A. Racoosin, MD, MPH
Thomas P. Laughren, MD
Russell Katz, MD

From the Division of Neuropharmacological Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland

EL 2001

David Campana,
Alaska Medicaid Pharmacy Program Manager

September 19, 2007

Q. Has Eli Lilly ever made misrepresentations about the safety, efficacy, effectiveness of Zyprexa to the State of Alaska?

A. Not that I know of.

Tr. 298, ln.12-15

David Campana,
Alaska Medicaid Pharmacy Program Manager

September 19, 2007

Q. As of March 2006, did you have anything that you would base your contention that the package insert was a misrepresentation of -- misrepresentation to the State of Alaska that Zyprexa was safe and effective?

A. No.

Tr. 300, ln. 3-7