

Partnering with Customers to Address Diabetes Concerns

Background and Key Message Elements:

Approximately 7.8% of the general adult population had diabetes (one-third of which was undiagnosed) as reported in an epidemiological study of prevalence in the US. An additional 6.9% of the general population had fasting plasma glucose levels above normal in the same study. Diabetes is a significant and growing world health issue. By 2025, the total number of American adults with diabetes is estimated to reach 21.9 million, with an estimate of 300 million adults worldwide. About 10% of patients with diabetes have Type 1 defined as very low or virtually absent insulin production requiring exogenous insulin, while about 90% have Type 2 characterized by both insulin resistance and relative insulin deficiency. For our purposes, we are concerned with Type 2 and will refer to it hereafter as diabetes. In addition to obesity, which weight gain with antipsychotics can contribute to, there are numerous risk factors to assess, such as family history, ethnicity, lack of exercise and a high-fat diet. The prevalence of diabetes among patients with schizophrenia and bipolar disorder was as high as 2-4 times greater than in the general population in several studies.

The American Diabetes Association (ADA) recommends screening every 3 years for all people over the age of 45 by measuring a fasting plasma glucose. Patients with risk factors or symptoms should be screened at a younger age and/or more frequently. Common symptoms include increased thirst and hunger, increased urination and tiredness. In addition, the American Association of Clinical Endocrinologists (AACE) recommends that screening begin at age 30 in asymptomatic individuals with risk factors for diabetes. This recommendation clearly applies to most patients with severe mental illness.

Diabetes is a complicated disease state. Customers may base their concern on one or multiple factors. Therefore, it is critical we establish dialogue with the customer to pinpoint this concern, so we can address it using the most relevant data. Tone is critical. We need to be empathetic and not downplay the seriousness of diabetes or deny it is an important issue. However, we must be firm that although patients on Zyprexa may develop diabetes, they will do so at rates that are comparable to patients on other agents. Epidemiological studies indicate comparable rates of diabetes among patients treated with commonly prescribed antipsychotics and direct causality has not been established.

The reported differences in prevalence rates between antipsychotic medications are very small when compared to the absolute risk of developing diabetes that is associated with having a severe psychiatric illness. Given this, our customers should assess risk factors and monitor all patients appropriately, regardless of agent chosen.

With all of the competitor noise on weight gain and diabetes in the marketplace, we need to help customers put the focus back on efficacy. Market research indicates that efficacy is still far more relevant to the prescribing decision for Zyprexa than are diabetes or weight gain. When asked to rank the importance of 9 key parameters around prescribing decisions, customers ranked diabetes #9 behind EPS.

The primary considerations for choosing an antipsychotic should be its overall risk/benefit profile- that is- its efficacy in treating the psychiatric illness and its overall tolerability. Because of the amount of co-morbidity in patients with severe and persistent mental illness, we need to let our customers know they can count on Lilly to provide guidance and assistance in managing risk factors for diabetes and in enabling patients to obtain appropriate care.

Approaches to Handling Various Customer Concerns:

Clinical Experience – Customer has treated patients who have developed hyperglycemia, insulin resistance, diabetes or diabetic ketoacidosis (DKA) while taking Zyprexa.

- Hyperglycemia, insulin resistance, diabetes and DKA are related but different issues. Our customers may not clearly understand how each is defined and diagnosed.
 - Hyperglycemia: It is a relative term used to describe abnormally high glucose levels. The term may sometimes be used interchangeably with insulin resistance. The ADA has noted that a post-meal glucose level rarely exceeds 140 mg/dL in non-diabetic individuals. An individual with hyperglycemia may not necessarily be symptomatic with glucose levels in this range. Keep in mind that hyperglycemia is a reflection of what the blood sugar is doing at the time of the blood draw and there are many intrinsic and extrinsic factors that can influence this. Along with food or drink there are other disease states that can affect glucose levels. Among these are liver disorders, pancreatic disorders and alcoholism, not to mention general physical stress brought on by illness and/or infection. Think of hyperglycemia like a fever. It is a sign that something may be wrong, but it does not define a particular disease state.
 - Insulin Resistance: Insulin resistance has been defined as a plasma glucose level ≥ 110 mg/dL but < 126 mg/dL (fasting test) and ≥ 160 mg/dL but < 200 mg/dL (random test). It occurs when the cells do not respond well to insulin meaning it takes more and more insulin to accomplish the task of transporting glucose into the cell, thereby increasing the amount of sugar that stays in the blood stream. This persistent increase in blood glucose levels leads to hyperglycemia and potentially diabetes. Although obesity is thought to be a risk factor, the obesity associated with insulin resistance is very distinct. It is referred to as “trunkal” obesity where patients carry their weight mainly in the torso. Not everyone predisposed to insulin resistance goes on to develop diabetes. In fact, about 25% of the normal population may be insulin resistant and with proper diet and exercise may not experience hyperglycemia and/or diabetes.
 - Diabetes: The ADA recommends the use of a fasting plasma glucose test to screen for diabetes. The AACE and ADA recommend that a diagnosis of diabetes can be made when any of the following methods is used AND confirmed on a subsequent day:
 1. Fasting plasma glucose ≥ 126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours.

or

2. Symptoms of diabetes plus random plasma glucose concentration ≥ 200 mg/dL. Random is defined as any time of day without regard to time since last meal. Common symptoms include tiredness, increased thirst or hunger and increased urination.

or

3. Two-hour post load plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test. This test is more strenuous and is generally used to confirm suspected diabetes.

Note: Glycosylated hemoglobin A1c (HBA_{1c}) levels are useful for monitoring the long-term control of diagnosed diabetes but are not recommended for screening or for the diagnosis of diabetes.

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- **DKA:** DKA is far more common in Type 1 diabetes but may occur in Type 2. DKA occurs when an insulin deficiency leads to insufficient amounts of glucose being taken into the cells to produce energy. The body then resorts to other sources of energy (e.g., break down of muscle tissue). This process can lead to organ failure and other complications. DKA can be life threatening with mortality estimated to be 3 to 10%. It is often characterized as unpredictable and causing sudden, inexplicable death. However, when cases of DKA are explored, it has been found that pre-existing, undiagnosed or poorly controlled diabetes are often confounding factors.
- The following information pertains to adverse events spontaneously reported by patients during Phase 2 and 3 clinical trials as listed in the "Precautions" section of the FDA approved package insert. The frequencies presented represent the proportion of patients exposed to multiple doses of the study drug who experienced an event of the type cited on at least one occasion while on the study drug. It is important to emphasize that, although the events reported occurred during treatment with the agent, they were not necessarily caused by it. Additionally, these data cannot be used to predict the incidence of side effects in the course of usual clinical practice or to make comparisons among treatment options. An "Infrequent" adverse event is defined as occurring in 1/100 to 1/1000 patients, while a "rare" event is defined as occurring in less than 1/1000.
 - Zyprexa (4189 patients): Listed under "Other Adverse Events" as "infrequent" are hyperglycemia, hypercholesteremia, hyperlipemia and diabetes and as "rare" is DKA.
 - Risperdal (2607 patients): Listed under "Other Adverse Events" as "infrequent" is diabetes and as "rare" is hypertriglyceridemia; Diabetes mellitus aggravated, including diabetic ketoacidosis, is listed as an adverse event reported since market introduction which was temporarily (but not necessarily casually) related to Risperdal therapy.
 - Seroquel (2300 patients): Listed under "General" is "Patients had increases from baseline in cholesterol (11%) and triglyceride (17%) compared to slight decreases in placebo patients. These changes were only weakly related to the increases in weight observed in Seroquel-treated patients." Listed under "Other Adverse Events" as "infrequent" are hyperglycemia, hyperlipemia and diabetes.

- Geodon (3834 patients): Listed under “Other Adverse Events” as “infrequent” are hyperglycemia and hypercholesteremia and as “rare” are hyperlipemia and glucose tolerance decreased (i.e., insulin resistance?).
 - Depakote: There are no adverse events relating to diabetes or related disorders. However, there are black box warnings for hepatotoxicity, teratogenicity and pancreatitis.
- Present Diabetes Sell Sheet (OL21620) showing results from Zyprexa head-to-head studies vs. Haldol, Risperdal, Depakote, Clozaril and Geodon. Studies demonstrate comparable rates of treatment emergent diabetes and random/fasting blood glucose elevations among the agents.
 - Use the “human body” chart to show mental illness, ethnicity, family history, lack of exercise, obesity and other variables play a role. Therefore, weight and diabetes should be carefully monitored in every patient regardless of medication.
 - Show statistics indicating that diabetes is common in the general adult population, and is more common in patients with psychiatric illness.
 - Present the findings from 4 epidemiological studies using the sell sheet (OL21619). Two Janssen and 2 Lilly studies show Risperdal and Zyprexa as having comparable incidence and odds ratios of developing diabetes (range 1-3%).
 - Use clinical experience verbatim in response to unsolicited questions:
 - Doctor, your clinical experience is extremely important. However, your experiences seem to differ from large-scale clinical studies. Do you mind if we explore some potential reasons for this difference?
 - I’ve had this question from other physicians. When we dug deeper into the issue, we found a couple reasons why this may be the case. First, some physicians were more selectively assessing Zyprexa patients for hyperglycemia or diabetes. When they began to assess patients on other medications, they began to uncover additional cases. Second, other physicians have realized their perceptions have been influenced by the fact that they have significantly more patients on Zyprexa than other agents.
 - Another possibility may be that your patient population could be different. For example, you may be treating a more severely mentally ill population that could be at an even greater risk of diabetes, and you may be using more Zyprexa in those patients than other medications.
 - As we move forward, I would ask that you assess all of your patients on psychotropic medications. Most physicians who assess all their patients for diabetes find that the incidence is comparable, and low, among the agents.

Weight Gain With Zyprexa Leads to Diabetes and/or Other Co-Morbidities – Customer is concerned that weight gain with Zyprexa will lead to diabetes and/or other co-morbidities like hypercholesteremia and hyperlipemia.

- Present the Diabetes Sell Sheet (OL21620) to establish weight as just one of many risk factors:
 - Use the “human body” chart to show mental illness, ethnicity, family history, lack of exercise and other variables play a role. Therefore, weight and diabetes should be carefully monitored in every patient regardless of medication.

- Show statistics indicating that diabetes is common in the general adult population, and is more common in patients with psychiatric illness.
 - Show results from Zyprexa head-to-head study with Geodon in which the 2 agents had comparable, and clinically insignificant, elevations in fasting glucose levels over 6 weeks despite the fact that Zyprexa patients had a statistically higher mean weight gain compared to Geodon in that study (8 vs. 2 lbs.).
 - Discuss the two “pie” charts indicating that 79% of those patients who had an episode of hyperglycemia did not experience substantial weight gain, while 96% of patients with substantial weight gain had no glycemc abnormalities at all.
- Because obesity is a risk factor, we need to put Zyprexa’s weight gain into perspective and demonstrate that it is predictable and manageable.
- Use the Kinon reprint “Long-Term Olanzapine Treatment: Weight Change and Weight-Related Health Factors in Schizophrenia” to discuss overall weight change findings:
 - Mean weight gain in patients observed for a median of 2.54 years trended toward a plateau after the first 39 weeks of treatment with a mean weight change of 13.8 lbs.
 - Patients with higher BMI gained significantly less weight than lower BMI patients.
 - Weight gain was not dose dependent. Establishing this is critical to our appropriate dose message strategy!
 - 70% of patients either lost weight, remained stable or gained up to 22 lbs.
 - Some customers may avoid certain patients (e.g., obese) or switch those who are responding to Zyprexa to a different medication due to weight gain, risk of diabetes or related concerns. While this may be the best option for select patients, we need to be sure the customer is fairly assessing the risks and benefits. Weight gain is a potential adverse event for most medications used to treat severe mental illness. While weight gain liability may vary among the agents (see below), the data indicates diabetes occurs at comparable rates. More importantly, there is no guarantee a patient will experience the same therapeutic response on a different medication (e.g., see Seroquel vs. Haldol, Zyprexa vs. Haldol and Zyprexa vs. Risperdal studies by Arvanitis, Tollefson and Tran, respectively). According to FDA approved PI’s, a greater than 7% increase in weight from baseline to endpoint occurred at the following rates:
 - Zyprexa 29% vs. placebo 3% in 6 week studies; Note: weight gain was **NOT** listed as a dose-related adverse event;
 - Risperdal 18% vs. placebo 9% in 6 to 8 week studies; Note: weight gain was listed as a dose-related adverse event;
 - Seroquel 23% vs. placebo 6% in 3 to 6 week studies; Note: weight gain was listed as a dose-related adverse event; this is an important consideration in chronic schizophrenic patients for whom higher doses are generally recommended;
 - Geodon 10% vs. placebo 4% in 4 to 6 week studies; Note: weight gain was **NOT** listed as a dose-related adverse event;
 - Depakote weight gain was not presented using “7%” criterion. However, the 47 week extension study comparing Zyprexa to Depakote showed statistically greater weight gain with Zyprexa early in treatment but no statistical difference after week 15. Patients on Depakote may experience nausea early in therapy (10.4% Zyprexa vs. 28.6% Depakote) that could explain the lower initial weight gain.
 - Use the “rapid weight gain” chart in the sales aid (OL24830) to show predictability:

- Explain the 15% and 85% curves appropriately. That is, 15% of the patients fell on the “rapid weight gain” curve indicating the patient gained 7% or more of their baseline weight at 6 weeks. Not all patients are going to experience excessive weight gain. However, rapid weight gain can be a good early predictor of those patients who may be susceptible to gaining excessive weight. Therefore, about 15% are going to need significant early intervention to keep them from gaining excessive weight. Stay away from words like “just” or “as little as” 15% because physicians may feel we are minimizing the issue.
- 85% of patients fell on the “non-rapid weight gain” curve and gained an average of 5 lbs. The majority of patients will gain SOME weight on Zyprexa. However, for the vast majority, it will be a manageable amount of weight. Let’s be very clear, this does NOT mean that 85% of patients don’t gain weight!
- Offer the customer “How-To’s”: If you see a 2 lb. or greater weight gain on average per week, then the customer may want to strongly consider an early intervention. Offer weight management solutions using our available tools. While behavioral interventions are preferred, there may be some customers, or patients, who may also be interested in pharmacological interventions like Axid. If the customer inquires about these approaches, then send a medical letter.

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- Use the weight management solutions sell sheet (OL21709) to show weight is manageable using simple interventions.
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- Nguyen Study: 2.5-20 mg/day dose range; the average dose of the patients who lost weight was 15.8 mg/day.
- Littrell Study: 15 and 18 mg/day; weight change of 1-6.4 lbs.
- Ball Study: 15-40 mg/day; patients lost weight in Weight Watchers program.
- Key finding: The patients who were most successful managing their weight tended to be on the highest doses of Zyprexa. Are they able to manage weight because Zyprexa at the appropriate dose is helping them manage their illness?

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- Present the Kinon study to show Zyprexa's effect on other health factors:
 - Medium serum glucose at endpoint was not significantly associated ($p=.096$) with weight change for Zyprexa.
 - Medium serum cholesterol and diastolic blood pressure for Zyprexa-treated patients at endpoint showed a relationship with weight change that was statistically ($p \leq .001$) but not clinically significant based on the ranges observed.
 - The difference in incidence of elevated serum glucose, cholesterol, or diastolic blood pressure of Zyprexa vs. Haldol therapy groups was not different ($p > .05$).
- Regarding health factors, following are key findings from Pfizer's 6-week acute schizophrenia study of Zyprexa vs. Geodon, the results of which are presented in the Geodon sales aid:
 - The 6-week study shows Zyprexa having a statistically higher mean weight gain (8 vs. 2 lbs.), median change in fasting total cholesterol (19.5 mg/dL vs. -1 mg/dL), median change in fasting LDL cholesterol (13 vs. -1 mg/dL), median change in fasting triglycerides (26 vs. -2 mg/dL) and median change in fasting insulin (3.3 vs. 0.25 microunits/mL) with no significant difference in median change in fasting HDL cholesterol or fasting glucose response.
 - This 6-week study was extended out to 6 months and the results shared in a poster presented by Dr. George Simpson and colleagues. At 6 months, the investigators show greater mean weight increase with Zyprexa. However, they do not find a difference in insulin levels. Mean total cholesterol did increase more in the Zyprexa group, albeit not statistically significantly different from the Geodon group. Triglyceride results are not mentioned in the 6-month report.

Weight Gain With Zyprexa Can Lead to Insulin Resistance and Eventually Diabetes –

Customer is concerned that weight gain with Zyprexa can lead to insulin resistance, which, in turn, can lead to diabetes.

- See "Weight Gain" section above.
- Use verbatim:
 - Insulin resistance occurs when the normal amount of insulin secreted by the pancreas is not able to turn on the mechanism by which glucose is transported into the cells. In fact, diabetes can either be characterized as an insulin deficiency, where the pancreas does not produce enough insulin or insulin resistance, which means the cells do not respond well to insulin (i.e., it takes more and more insulin to accomplish the task of transporting glucose into the cell, thereby increasing the amount of sugar that stays in the blood stream). This persistent increase in blood glucose levels leads to hyperglycemia and/or diabetes.
 - The exact cause of insulin resistance is unknown. Heredity is thought to play a role as well as obesity and lack of physical exercise. Although obesity is thought to be a risk factor, the obesity associated with insulin resistance is very distinct. It is referred to as "trunkal" obesity where patients carry their weight mainly in the torso. Not everyone predisposed to insulin resistance goes on to develop diabetes. In fact, about 25% of the normal population may be insulin resistant and with proper diet and exercise may

- Present the findings from 4 epidemiological studies using the sell sheet (OL21619). Two Janssen and 2 Lilly studies show Risperdal and Zyprexa as having comparable incidence and odds ratios of developing diabetes (range 1-3%).
- While we do not want to contradict our position that case reports are not sufficient to define risks and draw correlations, it is important to point out there are case reports of hyperglycemia, diabetes and DKA in patients treated with other agents, including Clozaril, Zyprexa, Risperdal and Seroquel. For reference purposes, some reviews are listed:
 - Drs. Elizabeth Koller (Division of Metabolic and Endocrine Drug Products at the FDA) and Murali Doraiswamy, identified 237 reports of spontaneous adverse events of hyperglycemia or diabetes occurring in Zyprexa treated patients (*Pharmacotherapy* 2002). One hundred ninety-six cases between Jan '94 and May 15 '01 were identified with the US FDA's MedWatch Drug Surveillance System, and 41 cases published through May 15, '01, were identified with MEDLINE or through meeting abstracts. Of the 237 cases, 188 were new-onset diabetes, 44 were exacerbations of preexistent disease, and 5 could not be classified. Seventy-three percent of all cases of hyperglycemia appeared within 6 months of start of Zyprexa therapy. Eighty patients had metabolic acidosis or ketosis, 41 had glucose levels of 1000 mg/dL or greater, and 15 patients died. When Zyprexa was discontinued or the dosage decreased, 78% of patients had improved glycemic control. Hyperglycemia recurred in 8 of 10 cases with rechallenge. Authors' conclusions: Number of reports, temporal relationship to start of Zyprexa therapy, relatively young age, and improvement on drug withdrawal suggest that Zyprexa may precipitate or unmask diabetes in susceptible patients.

Talking points in response to unsolicited questions:

- Drs. Koller and Doraiswamy are calling attention to the very important issue of co-morbidity of diabetes in patients with serious mental illness. Diabetes is common in psychiatric patients and, as in the general population, it tends to develop insidiously over many years. Recent work presented by Lilly researchers at the June '02 ADA meetings demonstrated that patients with treatment emergent diabetes on various psychotropics, including Zyprexa, tended to be those patients with abnormal glucose control or diabetes risk factors even before starting treatment. Therefore, we strongly believe that vigilance is important when prescribing all psychotropic agents.
- The *Pharmacotherapy* journal article is one of many articles Drs. Koller and Doraiswamy are publishing on the topic; they've previously presented data on co-morbid diabetes in Clozaril patients in an American Journal of Medicine article in late '01 and they presented a poster on Risperdal and diabetes complications at the Endocrine Society meeting in June '02.
- In the Risperdal abstract, the authors conclude there are similar reports of hyperglycemia with Risperdal, Zyprexa, Clozaril and Seroquel and suggest that the "antipsychotic use may unmask or precipitate diabetes in psychotic patients". However, they also report that no conclusions on causality or relative risk between agents can be drawn without further studies.
- We agree that the relationship of diabetes, psychiatric illness and antipsychotics is unclear. Because Lilly is deeply committed to the well-being of patients, we are continuing to diligently investigate the issue

through head-to-head studies, epidemiological data and gold-standard endocrine studies, including the "Hyperglycemic Clamp" study. These studies have not established any causal linkage.

- We also support an ongoing review of all frequently prescribed antipsychotics for risk of diabetes. It would be misleading and ultimately harmful to patients to imply that certain antipsychotics keep patients safer from diabetes than others. Since head-to-head studies and epidemiological data show comparable rates of diabetes among agents, and co-morbid diabetes is common with all frequently prescribed agents, we believe that vigilance in assessing and educating mentally ill patients on diabetes is essential, regardless of agent chosen.
- Dr. Elizabeth Koller identified 132 reports of spontaneous adverse events of hyperglycemia occurring in Risperdal treated patients between Jan. '93 and Dec. '01 (presented as clinical science poster at The Endocrine Society meeting in June '02). Eighty-three patients had newly diagnosed hyperglycemia, 40 had exacerbation of preexisting disease and 9 could not be classified. Severity of reported cases ranged from mild glucose intolerance to DKA or hyperosmolar coma. There were 36 cases of acidosis or ketosis, 5 patients died. Authors' conclusions: Causality cannot be ascertained due to the nature of these data and absence of control groups. While the number of such cases in the literature and in Medwatch attributed to Clozaril and Zyprexa are greater than those with Risperdal, no conclusions can be made until direct prospective studies of causality and relative risk are done.
- Dr. Donna Wirshing (UCLA and West LA VA) published 2 retrospective cases in which patients with schizophrenia developed diabetes while taking Risperdal (*Society of Biological Psychiatry* 2001). [Similar to reported cases with Zyprexa] both patients had preexisting risk factors for diabetes and developed insulin resistance in the context of weight gain. Both cases necessitated medical intervention and one patient requires ongoing treatment with insulin. Authors' conclusions: Although the exact mechanism of antipsychotic induced diabetes remains obscure, weight gain appears to be a significant risk factor. Careful monitoring of weight and fasting glucoses is recommended for any patient taking novel antipsychotic medications.
- Drs. Domon and Cargile (Arkansas State Hospital) published a case report of Seroquel-associated hyperglycemia and hypertriglyceridemia in a 17-year-old African-American female (*Journal of American Academy of Child and Adolescent Psychiatry*, May '02). Her diagnosis included bipolar disorder, conduct disorder and mild mental retardation. Psychotropic medications at time of presentation included divalproex (1500 mg/day for more than 8 months), Seroquel (600 mg/day for more than 3 months) and Paxil 20 mg/day (for 1 day). One to 2 months following initiation of Seroquel therapy, diabetes was diagnosed. Her serum glucose levels approached 300 mg/dL and her fasting triglyceride level was 456 mg/dL. She did not experience significant weight gain during the 3 months of Seroquel therapy. Seroquel was tapered over 1 week and discontinued because she had not responded as robustly as hoped and because her hyperglycemia and hypertriglyceridemia apparently developed after the initiation of Seroquel. The patient demonstrated improved serum glucose control after Seroquel was discontinued.

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If asked an unsolicited question regarding the Japan Label change, use verbatim:

- The package insert for Zyprexa in Japan has been modified instructing physicians not to use Zyprexa in patients with pre-existing diabetes, and includes a warning statement that some patients may experience a marked increase in blood glucose during Zyprexa administration.
- The label change in Japan was based on 9 cases of severe hyperglycemia, including two deaths. This comes from a total estimated patient exposure in Japan of 137,000 patients since launch in June '01 (representing less than .01% of patients treated with Zyprexa in Japan, which is consistent with the Zyprexa PI). Most of these 9 patients had known or suspected pre-existing diabetes. All 9 involved other factors, such as family history of diabetes or concomitant acute medical illness. In the 2 cases that resulted in death, it appears that the fatalities may have been prevented with standard monitoring and treatment.
- The Asians in general and the Japanese in particular are thought to be one of the ethnic groups that are at elevated risk for diabetes. However, if you look at the case reports at hand, many of the patients had diabetes or co-morbid risk factors before taking Zyprexa. We believe the real difference in Japan is with the regulatory environment. Unlike in the US, members of the Japanese regulatory body can be held personally liable for an adverse event and, therefore, regulators tend to be more conservative. In this situation, they based their decision on looking at 9 serious case reports. We disagree with this decision because we have examined evidence across 8 million Zyprexa patients worldwide and have found no causal association or any difference in rates of diabetes with other drugs.
- In July '02 and September '02, Astra-Zeneca/Fujisawa and Janssen presumably volunteered a label change on quetiapine and risperidone in Japan, respectively, to include hyperglycemia in the "Other Adverse Reactions" section.

Clinical and Epidemiological Studies – Customer is concerned about published or unpublished studies that show a greater risk of diabetes with Zyprexa.

- It is important to first understand what study has led to the customer's concern. Most competitor studies are un-blinded, poorly controlled, small sample size and contain biased treatment selection (e.g., in the Newcomer study, the Zyprexa group contained mostly African Americans, which is a higher risk group). Additionally, many published articles are

literature reviews with no new data that our competitors are using to create more noise. For example, Pfizer is distributing a literature review article published in the October '01 issue of *JAMA* entitled "Drug-Induced Hyperglycemia".

- See package insert information in the "Clinical Experience" section above.
- Present Diabetes Sell Sheet (OL21620) showing results from Zyprexa head-to-head studies vs. Haldol, Risperdal, Depakote, Clozaril and Geodon. Studies demonstrate comparable rates of treatment emergent diabetes and random/fasting blood glucose elevations among the agents.
 - Use the "human body" chart to show mental illness, ethnicity, family history, lack of exercise, obesity and other variables play a role. Therefore, weight and diabetes should be carefully monitored in every patient regardless of medication.
 - Show statistics indicating that diabetes is common in the general adult population, and is more common in patients with psychiatric illness.
- Present the findings from 4 epidemiological studies using the sell sheet (OL21619). Two Janssen and 2 Lilly studies show Risperdal and Zyprexa as having comparable incidence and odds ratios of developing diabetes (range 1-3%).
- If asked an unsolicited question about the *British Medical Journal* article (*Assessment of Independent Effect on Olanzapine and Risperidone on Risk of Diabetes Among Patients With Schizophrenia: Population Based Nested Case-Control Study*, Aug '02; Koro et al), use verbatim:
 - The author concludes that patients taking Zyprexa had a significantly increased risk of developing diabetes than non-users of antipsychotics and those taking conventional antipsychotics, whereas Risperdal did not.
 - Although the study is not powered to compare Risperdal and Zyprexa, there is probably NOT a significant difference between them.
 - The investigators found almost 300 patients who developed diabetes on conventionals but only 7 on Zyprexa and 7 on Risperdal, so it is really difficult to draw conclusions about Zyprexa and Risperdal based on this small number of cases.
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 - Given that diabetes is 2-4 times more likely in persistently mentally ill patients, it is a serious co-morbid issue in this population. Treatment selection does not protect patients from diabetes and it would be a disservice to patients to recommend to physicians anything other than assessing all their patients on antipsychotic medications for diabetes.
- If asked an unsolicited question concerning the Sernyak study (*Association of Diabetes Mellitus with use of Atypical Neuroleptics in the Treatment of Schizophrenia, Am J Psychiatry, April 2002*), use verbatim:
 - This is a useful study because it highlights diabetes as an important concern for patients with schizophrenia and does so irrespective of which atypical antipsychotic is being used. However, because this is a retrospective prevalence (vs. incidence) study

looking at a 4-month snapshot of 38,000 Veterans with schizophrenia, it does not establish a causal relationship between the medication being administered and the incidence of diabetes. No consideration was given to existing medical conditions such as obesity, family history, etc. The authors do point out that diabetes risk may be linked to the severity of the underlying psychotic condition. In other words, for various reasons severely ill patients may be more likely to develop diabetes than those with less severe psychotic disorders. Because of its efficacy, Zyprexa is often the first choice medication for those sicker patients.

- Nevertheless, rates of diabetes on Zyprexa were slightly numerically higher than on Risperdal, but lower than on Clozaril and Seroquel. These differences were not statistically significant. Therefore, this study is consistent with other studies that suggest the risk for the developing diabetes in patients with schizophrenia is comparable across atypicals. The primary considerations for choosing a psychotropic should be its risk/benefit profile - that is - its efficacy in treating the psychiatric illness and its overall tolerability.
- If asked an unsolicited question on the Newcomer study (*Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia, Archives of Gen Psychiatry, April 2002*), use verbatim:
 - The Newcomer study actually showed a similar pattern for Zyprexa and Risperdal and did not report any significant differences between them. It did report glucose levels numerically higher on Zyprexa, but that may simply reflect small sample size, unblinded and non-randomized study design, length of treatment differences between inpatient and outpatient groups, and the fact that the Zyprexa group was comprised of mostly African-Americans, a higher risk group, and had 3 patients on concomitant valproic acid.

Zyprexa Affects Insulin Secretion – Customer is concerned that Zyprexa adversely affects the ability of the pancreas to secrete insulin, thereby resulting in hyperglycemia or diabetes.

- If asked an unsolicited question, present the TED (Clamp) study “Risk Factors for Treatment Emergent Glucose Abnormalities in Patients with Schizophrenia” (Sowell et al, Twenty-third Congress of the Collegium International Neuro - Psychopharmacologicum June 23-27, '02; Montreal, Canada) using the verbatim:
 - Study explores whether there is a direct effect of ZYPREXA on the pancreas, which could lead to differences in risk for diabetes or risk for DKA.
 - Insulin and glucose levels were measured in normal volunteers before and after treatment with Zyprexa, Risperdal and placebo. This is a strenuous test, the gold standard in endocrinology, and is not customarily performed in patients with a severe illness like schizophrenia. If healthy volunteers had performed poorly in this test it would have clearly signaled a direct link with the agent.
 - Blood glucose levels were held constant at 200 mg/dl for 4 hours, while insulin and glucose levels were periodically measured.
 - Results: The study showed no impairment in the pancreas' ability to secrete insulin regardless of agent tested. In fact, the results were very similar on Zyprexa and Risperdal.

References include Knowledge Management, Brand Team, FDA package inserts, various journal articles cited herein and thought leaders, including Drs. Donna Wirshing and Jambur Ananth, UCLA.

Tom Williams
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Updated 10/14/02