

# Policy Committee Pre-Read: Update on Zyprexa

## June 9, 2003

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### Overview

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The following topics are covered in this document:

- **APA: key events and learnings**
- **Marketplace perceptions of Zyprexa endocrine profile**
- **Diabetes data and regulatory environment**
- **Action plans and key initiatives to address diabetes perceptions**
- **Abilify update**
- **Zyprexa and Access**
- **New opportunities for differentiation on the horizon**
- **Summary of key takeaways**

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### APA 2003: Key Learnings

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This year's APA was marked by a significant emphasis on (1) bipolar disorder, (2) weight gain and diabetes, (3) attempts to commoditize efficacy, and (4) overall limited media coverage for the event.

The Lilly-sponsored symposium on bipolar disorder was acclaimed by attendees to be outstanding in terms of quality and breadth of data. With expected 2003 launches of new indications in bipolar mania, Astra Zeneca (Seroquel) and Janssen (Risperdal) seemed to have a strategy of providing much less significant data of their own and use Zyprexa data to establish a "me-too" carry-over of equity.

BMS' Abilify had a significant booth and overall commercialization presence. Their major focus was on commercializing a study with an outcome of "Aripiprazole Demonstrates Better Weight Change Profile, Comparable Efficacy in Schizophrenia Compared to Olanzapine." While the study is questionable in many respects, we can expect to see a high degree of emphasis on this data by BMS.

In the midst of APA, an article was published in the NY Times, "Leading Drugs for Psychosis Come Under New Scrutiny" questioning the value of atypicals vs. typicals. A poorly attended debate on this topic also occurred at APA. The lasting effect of these discussions does not appear to be significant given the real-world differences experienced by physicians and their patients. Significant additional media coverage has not occurred.

Lilly market research conducted during APA had some concerning themes. For some customers a "concern" about Zyprexa and diabetes has now become a "fear." In nearly all competitive symposia there was a significant emphasis on

Zyprexa – weight gain and diabetes. The intensity of repetition around this topic has reached “feverish” levels.

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### **Marketplace Perceptions of Zyprexa Endocrine Profile**

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We are observing a shift from “concern” to “fear” of patients developing significant weight gain and diabetes, and physicians own personal liability should that occur. It is an observable change.

Brand equity and the competitive and issues tracker market research suggest Zyprexa is disproportionately associated with issues such as weight change and diabetes.

We have seen a reduction in the number of patients staying on Zyprexa. Switching to other agents is occurring after the acute phase due to observed weight change or concern about metabolic issues. This switching is not as prominent in OUS markets; however, in some brand council affiliates it is becoming more of an issue.

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### **Diabetes Data and Regulatory Environment**

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New scientific data continues to support an elevated risk for diabetes in schizophrenia itself:

- Univ. of Buffalo study demonstrated elevated relative risk in 1940s prior to the introduction of antipsychotic drug (APD) treatment (20.9%) compared to current rates (10.4%) (Belliner, 2003)
- First episode, APD naïve patients have abnormal glucose tolerance and elevated fasting glucose and insulin levels (Ryan, 2003)

Several retrospective, epidemiology studies generally show no or little difference in diabetes rates between atypicals, although elevated rates between atypicals and traditional neuroleptics have been reported.

- Beth Koller (former FDA scientist) has now published four independent studies showing diabetes, DKA and related deaths associated with all commonly used atypicals: clozapine (12/01), olanzapine (7/02), risperidone (6/03) quetiapine (6/03). There were more cases in the clozapine and olanzapine analyses, which could be due to several factors: reporting bias, selection bias (sicker, more at risk patients), and weight gain differential.
- A new prospective VA study funded by BMS (but does not include Abilify) will show relative comparable rates among atypicals with strong evidence that the illness itself confers most of the risk as opposed to the drugs. This will be presented later in June 03. BMS is not pleased with the study results.

FOI access to the Abilify submission clinical trials package for FDA approval for their schizophrenia indication reveals one diabetic DKA death in Japan and low but comparable diabetes rates compared to olanzapine and haloperidol. This is important because of market place assertions of Abilify being the “clean” atypical.

Our two clamp studies (gold standard tests for causal mechanisms) performed in healthy volunteers and one independent clamp study in chronic schizophrenics (Newcomer, 12/02) has not shown a direct effect of olanzapine or risperidone on insulin secretion or on insulin receptors. These tests are very sensitive as demonstrated by studies of a single dose of a protease inhibitor (and other diabetes causing drugs) in healthy volunteers, which cause clear abnormalities in insulin receptor function. We currently have a prospective, clamp study in chronic schizophrenic patients underway.

Our treatment emergent diabetes study (Sowell, 2003) demonstrates that well characterized risk factors, especially glucose elevations at baseline, but not drug assignment, strongly predict the subsequent development of diabetes.

Because of our leadership, the ADA is moving forward with an academic consensus conference which will likely support the chronic mentally ill as an at risk population.

There is solid evidence that two key regulatory bodies, Canada and CPMP, are moving towards class labeling. This information was conveyed to us verbally from the regulatory leaders and therefore it would be inappropriate for us to publicize this information.

The FDA is very close to a position on glucose labeling as they are in the final stages of analyzing a VA PBM data set. Redacted

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## **Action Plans and Key Initiatives to Address Diabetes Perceptions**

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### **Sales force**

- The neuroscience sales force is launching the “Solutions for Wellness” personalized program in June to all customers. This is a weight management/exercise/healthy lifestyles program for patients. The pilot for this program was very successful:
  - Over 1900 patients enrolled in the top 5 states alone.
  - Over half of the states have a program completion rate > 30%

The data from the pilot prove that patients with schizophrenia and bipolar disorder can follow a healthy lifestyle program.

- The neuroscience retail sales force is rolling out a simplified version of the diabetes sell sheet to their customers the week of 6/9. “Comparable

rates” wording has changed to “*no consistent differences*” to increase message credibility. Some studies do show differences – though not clinically significant.

- Customer Communication Document – addresses Lilly’s position on Diabetes and litigation (late June). Note: Not for communication with analysts.
- New Buse PCS Reprint (Diamond Reprint) is being rolled out to the field 6/2003:
  - Patients treated with either conventional or atypical antipsychotics had a significantly higher risk of developing DM than the Advance PCS general patient population.
  - The risk of developing diabetes was comparable between conventional and atypical antipsychotic cohorts, as well as comparable between the risperidone and olanzapine cohorts.
- Pat Toalson Diabetes Presentation – A refresher course on diabetes in the mentally ill designed to increase sales representative confidence in handling diabetes concerns. Available in 24/7 playback or CD’ROM. Note: Not for communication with analysts.

### **Education**

- Continuation of Diabetes Education Program (program utilizing a certified diabetes educator to educate psychiatrists and treatment team members):  
Objective: Remove the fear from diabetes through education of targeted customers on how to assess, counsel and refer patients with co-morbid diabetes and mental illness.
  - 315 total programs completed thus far (136 in retail neuroscience).
  - Budget for an additional 10 programs per district through 12/2003
- Continuation “Ask the Experts” Issues DVD - sales representatives can utilize this tool with customers to help answer their concerns about diabetes in the mentally ill population.

### **Direct to Physician – Promotional**

- New Local speaker training on diabetes and litigation (Q3). Note: Not for communication with analysts.
- New downloadable resources for Health Care Professionals on Zyprexa.com (Q2/Q3).

- *New Neuro Treatment Team Partners Program “Health Checks”* module addressing all clinically significant aspects of psychotropic safety. Balances efficacy vs. safety. Sales reps can utilize this resource with customers. (Q3).
- *New Weight Management P2P* telesessions that highlight our resources to “help physicians help their patients manage weight” (Q3-Q4). Note: Not for communication with analysts.

#### **Direct to Physician – Non Promotional**

- Note: Not for communication with analysts.
- *New Direct Mail Diabetes & Weight Management Campaign* (Q2 – Q3).
- *New Diabetes Web-Conferences* for consultants (Q3-Q4).
- *New Continuing medical education offerings and enduring materials* (Q3-Q4).
- *Media Plan Highlighting Diabetes Data, Patient Successes & Lilly’s Resources* (Solutions for wellness and Diabetes Education Program)
- *Medical Liaison training* to discuss solutions for wellness and Diabetes Education Program with thought leaders (Q3).
- *Operation Restore Confidence*: Internal Lilly physicians will be meeting with key customers upon request to discuss Lilly diabetes data related to Zyprexa.

#### **Other Initiatives**

- Other initiatives are under consideration and will be discussed in more detail at the Policy Committee Meeting.

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#### **Abilify Update**

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The competitive framing around the diabetes issue has increased switches from Zyprexa to Abilify over the past five months. Abilify uptake has disproportionately affected Zyprexa as compared to other products.

Consistent with our expectations, Abilify is making its way on to formularies. Our strategy is to advocate for the placement of all atypical agents on formulary -- as long as Zyprexa is on the formulary with no restrictions.

#### **Review of Abilify Market Research:**

- Rapid uptake of Abilify is significant and not unlike the initial rapid uptake of Geodon. This indicates a pent-up need for a more tolerable schizophrenia agent. The question is whether we will see a flattening of

the Abilify adoption curve at the six-month point in the same way that Geodon flattened.

- Motivation for Abilify prescriptions are due in large part to concerns about Zyprexa with weight gain and diabetes.
- The switching does not appear to be drive by an inherent efficacy benefit that Abilify provides over Zyprexa.
- Physicians have indicated that they may be willing to sacrifice some efficacy to maintain a “more safe” side effect profile with Abilify.

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## **Zyprexa and Access**

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While maintaining access is intensifying as a challenge for Zyprexa, Kentucky and West Virginia remain the only two states that have prior authorized Zyprexa utilization for Medicaid recipients. Any successes we have in maintaining access must be considered temporary.

The influence of prescribers was attested to once again, when Massachusetts Medicaid officials discontinued a plan to tightly restrict patients' access to atypical antipsychotics, saying that even though the state could have saved millions of dollars, it was not worth the health risks to an extremely fragile population.

Specifics follow:

- Zyprexa is not restricted as a second line agent
- July 1st: All Atypicals are restricted to doses within their label
- July 1st: Use of multiple atypicals are restricted after 60 days

In West Virginia, where Zyprexa restriction went in to effect in April, we are working to address and solve the grand fathering issues with Zyprexa. We received a relaxation of “failure policies” for Zyprexa’s use in bipolar disorder.

In Maine, updated PDL was released with Zyprexa still in restricted status beginning July 1<sup>st</sup> implementation.

Texas legislation to create PDL and supplemental rebates is now in conference in house and senate. There is recent recognition from the state that value added programs can be considered as a potential option in lieu of rebates. We are positioning our disease management proposal similar to Massachusetts.

According to the access team in the U.S. Affiliate, there has been little pick up from payers on the NY Times article focusing on the typicals vs. atypical debate

Late last week, Tom Scully at CMS made comments that were picked up in the Wall Street Journal basically endorsing state purchasing coalitions as efficient and permissible mechanisms for states to save money in Medicaid on drugs. This will be an incremental challenge.

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## **New Opportunities for Differentiation on the Horizon**

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Over the next three quarters, we will have an opportunity to reinforce the “specialness” of Zyprexa relative to the competition on the basis of new indications and formulations:

- Re-launch of Zydys
- Redacted
- Launch of bipolar maintenance
- Launch of RAIM

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### Summary of Key Takeaways

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- This year’s APA was marked by a significant emphasis on (1) bipolar disorder, (2) weight gain and diabetes, (3) attempts to commoditize efficacy, and (4) overall limited media coverage for the event.
- We are observing a shift on the part of physicians from “concern” to “fear” of patients developing significant weight gain and diabetes, and physicians’ personal liability should that occur. It is an observable change.
- The U.S. Neuroscience sales force is utilizing all elements of the marketing mix to ensure we stop the erosion of Zyprexa.
- The competitive framing around the diabetes issue has increased switches from Zyprexa to Abilify over the past five months. Abilify uptake has disproportionately affected Zyprexa as compared to other products.
- The fact remains that as of today, only two states have restricted Zyprexa access. There continue to be many challenges facing the business to government group in ensuring free and unrestricted use of Zyprexa.
- There are several outstanding opportunities on the horizon to reinforce the “specialness” of Zyprexa in helping move lives forward: Zydys relaunch, Redacted bipolar maintenance launch, RAIM launch.