DATE: April 15, 2002

TO: All B2B Internal and External Personnel

FROM: Kristen Lynn Anderson (317-276-7919)
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RE: Zyprexa Label Change In Japan

The following is a verbatim that you may **proactively** discuss with your formulary decision makers.

Verbatim on Japan Label Change:

We received notice from the Japanese affiliate that the Zyprexa label in Japan will instruct physicians to not use Zyprexa in patients with diabetes or in patients with a history of diabetes, and will contain a warning statement that some patients may experience a marked increase in blood glucose during Zyprexa administration.

Lilly **strongly disagrees** with the conclusion drawn by the Japanese regulators, based on global scientific evidence of more than 8 million Zyprexa patient exposures. There have been 9 cases of severe hyperglycemia --including 2 deaths – reported in Japan. This comes from a total estimated patient exposure of 137,000 patients since their launch in June 2001, representing an incidence rate of less than .01%. All 9 cases involved other factors, such as personal and family history of diabetes and obesity, and the majority had known or suspected pre-existing diabetes. In the two cases that resulted in death, it appears the fatalities could have been prevented with standard monitoring and treatment.

For patients who develop diabetes, good clinical practice includes assessment and follow-up in accordance with local (e.g., ADA) guidelines. Given the evidence of comparable incidence of diabetes in patients with schizophrenia across commonly used psychotropic agents, such monitoring should be employed with all commonly used antipsychotics.

We expect this outcome in Japan will not affect the Zyprexa label in the United States.
It is important to keep in perspective the benefits of Zyprexa to patients with schizophrenia and bipolar mania.

Points to note

- This does not change the status of Zyprexa as a safe, effective and cost-efficient agent in the US market.
- In studies in the United States and Europe, the incidence of diabetes appears comparable across a wide variety of antipsychotic agents.[4,5,6]
- It is important to keep in perspective the patient and the health outcomes benefits of Zyprexa and other atypicals for patients with schizophrenia and bipolar disorder.

- Numerous studies at the state and local level have shown Zyprexa to be a cost efficient treatment in schizophrenia. This information regarding label changes in Japan does not affect the value of Zyprexa.

- Patient advocates and prescribers see value in ensuring all of the agents are available for the physicians to ensure the right drug is available for the right patient at the right time.

- Schizophrenia is devastating. Over 10 percent diagnosed with schizophrenia eventually commit suicide. Under these circumstances, the widest range of therapeutic options must remain available to patients. For many patients, Zyprexa is the therapy of choice.

4. Allison, DB, et al. Presented at: 2001 International Congress of Schizophrenia Research, Vancouver, British Columbia.
5. Cavazzoni P, et al. Presented at the 2001 Meeting of the New Clinical Drug Evaluation Unit, Phoenix, Arizona.
6. Fishbein H, Palumbo PJ: In Harris MI, et all (eds): *Diabetes in America* (National Diabetes Data Group). Washington, DC, National Institutes of Health, 1995, pp 283-291.

Additional background:

The Japanese regulatory agency has **not** mandated blood glucose monitoring for all patients on Zyprexa.

Tens of thousands of people with diabetes are being successfully treated with Zyprexa. Physicians should prescribe the agent that is best to treat the patient's mental illness, and address diabetes irrespective of the agent prescribed.

The unprecedented Japanese perspective, by unfairly singling out Zyprexa, could lead to a false sense of security among clinicians in their monitoring and treatment of patients with diabetes.

Events with an incidence of less than or equal to .01% are characterized by the FDA as "rare."

The Japanese label is inconsistent with U.S. and EU labels; specifically:

> The U.S. label notes hyperglycemia and diabetes as infrequent adverse reactions and diabetic acidosis (another name for diabetic ketoacidosis, or DKA) is listed as a rare occurrence.
>
> The EU label notes that hyperglycemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma have been reported very rarely. It states that appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes.

Lilly's fundamental position regarding incidence of hyperglycemia and/or diabetes across the antipsychotic class continues to be "comparable rates."

Excluding Japan, of the more than 8 million patients who've been prescribed Zyprexa, there have been 278 glucose-related events reported as of Sept. 30, 2001, or 1 per 23,536.

Lilly stands by its science, and is exploring several options to correct this regulatory injustice.