(P) olanz. hyperglyc.

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ATTACHMENT E

ZY 8032 1544

Olanzapine Labeling Change on Hyperglycemia
For 02/21/2000 GPLC Meeting

Proposal of the Product Team and PhV
Spontaneous reporting rate for hyperglycemia (<0.01%) is currently in the Core Data Sheet as a Core Adverse Event in the Adverse Drug Reaction table. **The proposal is to add the following information regarding hyperglycemia to the Core Data Sheet in C.8**: *New Statement* Random glucose ≥160mg/dL in patients with baseline random glucose ≥140mg/dL has been occasionally seen in clinical trials. *Revision* The frequency of hyperglycemia in the Adverse Reaction Chart will be changed: The postmarketing data for reported events will remain **<0.01%**, but the X will be designated with the # footnote. The clinical trial data for observed laboratory test results will be added to **<10% and ≥1%** and the X will be designated with the * footnote. **Note CIOMS definitions : <0.01%** *(very rare)* **<10% and ≥1%***(common or frequent)*

How Has this Proposal Arisen?
Recent review of random glucose levels of patients in olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia in olanzapine group (3.6%) was higher than that in the placebo group (1.05%). For common events, incidences from clinical trials provide more meaningful information

Product and Indication.
Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and other psychoses where positive and/or negative symptoms are prominent. Olanzapine is indicated for the treatment of acute manic or mixed episodes in bipolar disorder. The dosage range of olanzapine is from 5 mg to 20 mg per day

Current Labeling.

***UK SPC** section 4.8 rare (<1%)Undesirable effects:*
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases

***UK SPC** section 4.4, Special warnings and special precautions for use:*
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during ZYPREXA treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

USPI current label: Other Adverse Event section:
Endocrine System: infrequent: diabetes mellitus; rare : diabetic acidosis
Metabolic and Nutritional Disorders: infrequent: hyperglycemia, ketosis

Frequency of Exposure and Event.

	CONTROLLED CLINICAL TRIALS	POST-MARKETING EXPOSURE	TOTAL
# of patients with event	154 (laboratory observations)	237 (reported events)	N/A
# of patients treated	4234*	3,536,000e	N/A

Note: Postmarketing experience as of 9/30/99 from Review of Commercially Marketed (Spontaneous) Hyperglycemia Adverse Event Reports and Olanzapine January 2000 Note 332 patients identified, 237 verified with peak serum glucose
Note: Controlled Clinical trial number* **excludes *the patients who were randomized to other therapies prior to olanzapine, for whom there was a probable lab error, and those who were known diabetics at baseline.*

History of Observations. The first report of hyperglycemia associated with olanzapine was received in October of 1996 and the last report was received in September of 1999. The reporting frequency of the hyperglycemia has not changed over the 36 months of marketing (September 1996 through September 1999) olanzapine.

Case Histories. The spontaneous safety database for olanzapine has a large percentage of hyperglycemia cases in which the patient had a history of diabetes mellitus or significant risk factors for developing hyperglycemia. The spontaneous safety database also has a number of hyperglycemia cases in which the patient has no history or known risk factors for diabetes . Case DE98014684A involved a 35 year old male without a known history of diabetes who had received olanzapine 10mg daily for 6 months and developed hyperglycemia. The random blood sugar peaked at 400 mg% and the patient was hospitalized for control of the blood sugar. The concomitant medications were lithium and amitriptyline. Following hospitalization the olanzapine was discontinued and insulin therapy was initiated. Upon discharge the fasting blood sugars were < 100mg% and the insulin therapy had been discontinued. Olanzapine therapy was not restarted.

Other Studies. There are a number of small studies and references to hyperglycemia associated with atypical antipsychotics including olanzapine throughout the literature. These studies are referenced in Review of Commercially Marketed (Spontaneous) Hyperglycemia Adverse Event Reports and Olanzapine January 2000

Literature Reports. There are a number of papers published regarding hyperglycemia and olanzapine. One such article was published in Psychosomatics 40:5 in September 1999. New Onset Diabetes Mellitus and Diabetic Ketoacidosis Associated with Olanzapine Treatment described seven cases of new-onset diabetes mellitus that developed soon after initiation of olanzapine therapy. These cases are all found within the spontaneous safety database for olanzapine. Cases US97102155A, US_980503939, US_980503937, US971012230A, US97101204A, US_980503940, and US_980503942 are described within the article.

Dr. Daniel Casey from Oregon presented in a seminar at Lilly at the end of 1999. He performed chart review of 136 veteran patients who had been exposed to olanzapine therapy for at least 4 months (average of 1.4 year). Of the 39 patients who had normal fasting glucose levels before olanzapine therapy, seven (18%) had fasting glucose levels of 126 mg/dL or higher during olanzapine therapy (threshold that met the 1998 ADA diagnostic criteria for diabetes). Whether the glucose levels truly represented fasting results cannot be ascertained.

Pharmacology. It is not immediate apparent, based on the known pharmacology of olanzapine why it would cause hyperglycemia. The blockade of serotonin receptors by olanzapine along with its antihistaminic activity can explain associated weight gain. Though spontaneous reports suggest that hyperglycemia was more commonly reported by olanzapine patients who were obese, a definitive link between weight gain after olanzapine therapy and treatment-emergent hyperglycemia has not been established. Olanzapine and any resulting changes in insulin resistance has not been determined at this time. Glucose levels greater than 600 mg/dL was reported in half of the spontaneous reports of hyperglycemia. Such high levels cannot be explained readily by an increase in insulin resistance alone.

Class Effect. Olanzapine is classified as an atypical antipsychotic and has similarities to clozapine chemically and to clozapine, risperidone and quetiapine in terms of mode of action. The information from the Clozaril and Risperdal labels are displayed below. Reports regarding changes in blood sugar associated with cloazapine are found within the literature and noted in the labels.

	CLOZARIL	RISPERDAL
USA (USPI)	*Postmarketing experience* *<1%* *Miscellaneous* hyperglycemia;	Infrequent: Diabetes Mellitus *(under both pre and post-marketing experience)*

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UK SPC (1999-2000)	On rare occasions, hyperglycemia has been reported on patients on Clozoril treatment.	----------

Relationship to Dose. The spontaneous safety database has been evaluated for any dose response relationship regarding olanzapine and hyperglycemia. Given the information available there does not appear to be any relationship between hyperglycemia and the olanzapine doses.

Drug Interaction. There has not been any drug interactions identified that have contributed to the hyperglycemia associated with olanzapine.

Effect of Population.

Several studies have implicated schizophrenia as a potential risk factor for developing Type-II diabetes mellitus. Diet and lack of exercise associated with institutionalization, brain changes associated with schizophrenia, or a common underlying and linked pathology of schizophrenia and diabetes mellitus Type-II are possible explanations.

As in the general population, hyperglycemia was reported more commonly among blacks than Caucasians among schizophrenic patients who took olanzapine. Neither dose, age, gender, renal function, hepatic function or any other parameter appears to predispose the patient to hyperglycemia among the patients without history of diabetes or risk factors for such.

Position on Label. Recommend specific section of core label in which proposed wording should appear.
C.8 Undesirable Effects *New Statement* In patients with baseline random glucose less than or equal to 140mg/dL, hyperglycemia with random glucose greater than or equal to 160mg/dL has been observed during clinical trials. *Revision* The frequency of hyperglycemia in the Adverse Reaction Chart will be changed: The postmarketing data for reported events will remain **<0.01%**, but the X will be designated with the # footnote. The clinical trial data for observed laboratory test results will be added to **<10% and ≥1%** and the X will be designated with the * footnote. **Note CIOMS definitions : <0.01%** *(very rare)* **<10% and ≥1%***(common or frequent)*

Timeline for Submission:	
OPTIONS	MARK CHOICE
Submit the change immediately, but not later than 30 calendar days after GOLD distributes the change to affiliates (for changes involving a safety crisis or an urgent public health concern).	
Bundle changes according to an affiliate's registration plan. Submit the change as soon as possible, as consistent with affiliate practice, but not later than one year after GOLD distributes the change to affiliates	**X**
Other. Specify date _____.	

Timeline for Use in Packaging. Recommend the appropriate timeline for use in packaging, based on the following change implementation (effectivity) choices:	
OPTIONS	MARK CHOICE
Implement by a specified date _____ (may be used for urgent changes)	
Upon availability	**X**
Upon exhaustion, but not later than 6 months after a change is approved by a regulatory authority	
Other (used minimally)	

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Consultation Process		
REVIEWED BY	DATE	COMMENTS
Global Product Physician Charles Beasley	2/15/00	
GBU/Product Team		
Pharmacovigilance/Kenneth Kwong MD	2/15/00	
Other		