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Received:	Fri, 30 Nov 2007 15:50:46 +0000
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content-transfer-encoding:	quoted-printable

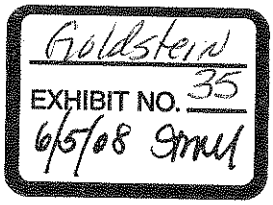
From: Goldstein, Jeffrey M

Sent: Wednesday, August 06, 2003 1:29 PM

To: Brian Martin; Callaghan, Cynthia; Daniels, Stephanie; Duff,David; Fetchko, Amy A; Gabriel, Linda; Hagger, Lynn; Hamill, Kevin; Hearn, Dionne; Hess, William; Law, Heather; Lloyd-Washington, Lisa; Macfadden, Wayne; Mueller, Karin; Mullen, Jamie A; Ney, Christine; Repp, Edward; Rubenstein, Vance; Sayce, Rod; Tugend, Georgia; Tumas, John A; Wilkie, Alison; Williams-Hughes, Celeste

Subject: FW: Seroquel Objection Handler- Koller et al abstract

Attachments: Koller-OH.doc



FYI

-----Original Message-----

From: Owen, Richard T

Sent: Wednesday, August 06, 2003 6:26 AM

To: +Seroquel Product Managers; +Seroquel MIO; +Seroquel Global Product Team; +Seroquel COT; +Seroquel Medical Managers

Subject: Seroquel Objection Handler- Koller et al abstract

Dear All

Please find attached an Objection Handler concerning the abstract presented by Koller et al on quetiapine associated diabetes at this year's APA meeting.

A PKT link to the objection handler is attached below

http://pkt.ta.astrazeneca.net/PKT_Library.asp?object_id=090082f18016b6ee&format=msw8&view=TRUE&recent=TRUE

Regards

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Objection Handler

Publication of abstract:
Koller E et al Quetiapine associated diabetes mellitus. Abstract presented at APA May 2003, San Francisco. [NR741]

Koller et al	Quetiapine-Associated Diabetes Mellitus	Abstract only
[2003][NR741]Quetiapine-Associated Diabetes Mellitus Elizabeth A. Koller, M.D., Endocrinology, University of Nebraska, 983020 Nebraska Medical Center, Omaha, NE 68198; P. Murali Doraiswamy, M.D., James T. Cross, M.S., Bruce S. Schneider, M.D. At the conclusion of this session, the participant should understand the potential for hyperglycemia with the use of the atypical antipsychotic quetiapine and how spontaneously reported adverse events can provide a signal for further investigation. Objective: Diabetes has been observed with older atypical antipsychotic agents, but the risks and clinical characteristics of hyperglycemia in patients treated with quetiapine remain unclear. Design: An epidemiologic survey of spontaneously reported adverse events in quetiapine-treated patients was conducted using reports from the Food and Drug Administration MedWatch surveillance program (1/1/97-8/15/ 02) and published cases. Results: We identified 46 reports of quetiapine-associated hyperglycemia and nine additional reports of acidosis that occurred in the absence of hyperglycemia. Of the reports of quetiapine-associated hyperglycemia, 34 patients had newly diagnosed hyperglycemia, eight had exacerbation of pre-existing disease, and 4 could not be classified. The mean (±SD) age was 35.3±16.2 years (range 5 to 76). New-onset patients (31.2±14.8 years) tended to be younger than those with pre-existing diabetes (43.5±16.4 years; p=0.08). The overall male:female ratio was 1.9. Most cases appeared within six months of quetiapine initiation. The severity of cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. There were 21 cases of ketoacidosis or ketosis. Eleven patients died. Conclusions: Atypical antipsychotic use may unmask or precipitate hyperglycemia. The onset may be rapid and severe. Although most cases occur soon after treatment initiation, risk is not eliminated with extended therapy. REFERENCES: 1. Domon SE, Cargile CS: Quetiapine-associated hyperglycemia and hypertriglyceridemia. J Am Acad Child Adolesc Psychiatry 2002; 41:495-496. 2. Sobel M, Jaggers ED, Franz MA: New-onset diabetes associated with the initiation of quetiapine treatment. J Clin Psych 1999; 60:556-557.		

- This abstract, based mainly on FDA Medwatch data claims to, but does not prove, a causal association between Seroquel and diabetes.
- There are several limitations concerning the data presented in the abstract and these are mentioned in this objection handler.

Aim of document
The aim of this document is to help the 'Seroquel' commercial team develop counter arguments to any potential adverse publicity generated by this publication.

Objection handler author	Dr Richard Owen, Global Medical Affairs Manager Date: 6 August 2003.
Input from	Dr Ron Leong US Drug Safety Physician

Key Points Summary

1. It should be appreciated that the prevalence of diabetes in the schizophrenic population (approximately 15%; Dixon 2000; Mukherjee, 1996) is higher than in the general population, approximately 10% (Mokdad, 2001).

2. Even drug-naive schizophrenic patients show impaired fasting glucose tolerance (Ryan 2003) and thus schizophrenic patients are at higher risk of diabetes.

3. From AZ Global Market Research we have estimates of cumulative exposure through 2002 of approximately 4 million patients in the US and 0.5 million for the rest of the world. The abstract doesn't indicate how many reports were US and how many were non-US. If we assume all 46 reports are from the US, we get 0.00115% (46 reports/4 million X 100 = 0. 00115%) If we assume some cases are from outside the US, the rate is less than what has been calculated. Even if one assumed there were 100 occurrences for every report in the FDA database the rate would be 0.1%- more than 100 fold less than the background prevalence of 15% in the schizophrenic population.

4. The reports in the abstract do not provide any details such as:
   (i) concomitant drugs associated with hyperglycaemia or diabetes
   (ii) risk factors such as obesity.
   (iii) for patients with a history of diabetes, compliance with a diabetes diet or medication or how well controlled the diabetes was before Seroquel

5. These were spontaneous reports and not from a controlled study and thus cannot be used to prove a causal relationship between Seroquel and diabetes or its complications. Since there was no control group, it cannot be ascertained whether these reports simply represent background occurrences of a common condition.

6. A review of AstraZeneca clinical study data showed no statistically significant differences in the least squares mean (LSM) change in random glucose measurements from baseline to endpoint between Seroquel and placebo in short term placebo-controlled trials (see Data on File 89). The claim: 'Seroquel is not associated with Type II diabetes' is mentioned in the Schizophrenia Sales Flow sent out earlier this year

References.

Dixon L et al Schizophrenia Bull 2000; 26: 903-912

Mukherjee S et al Comprehensive Psychiatry 1996; 37 (1): 68-73

Mokdad et al JAMA 2001; 286 (10): 1195-1200

Ryan MCM et al Am J Psychiatry 2003; 160 (2): 284-289