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To : Beamish, Don G; Brecher, Martin; Davies, Laura J; Doran, Nigel M; Leong, Ronald; Limp, Gerald L; MacFadden, Wayne; Minnick, Jim G; Remick, Rosemarie M; Schwartz, Jack A
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Subject : Privileged and Confidential: Master Q&A - Diabetes
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Custodians : Minnick, James

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Sent: 1/13/2004 11:19:59 AM
To: Beamish, Don G; Schwartz, Jack A; Davies, Laura J; Brecher, Martin; Doran, Nigel M; Leong, Ronald; Limp, Gerald L; Macfadden, Wayne; Minnick, Jim G; Remick, Rosemarie M
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Heather and I have worked with legal and provide for your reference, the attached updated "Master Q&A" document on the diabetes issue encompassing all other relevant matters associated with this topic. We will continue to update and add to this document as needed.

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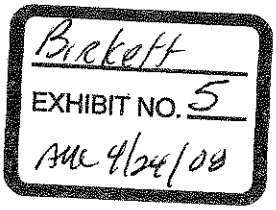

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Diabetes
Master Question and Answer Document

Diabetes General

1. Does SEROQUEL cause diabetes?

No. AstraZeneca believes that the available data do not establish a causal link between SEROQUEL and diabetes. Since its approval in 1997, there have been more than 6.1 million patient exposures to SEROQUEL worldwide. A retrospective analysis of 17,000 patients with psychosis revealed that those treated with SEROQUEL had estimated odds of receiving treatment for type 2 diabetes that were no more than those of untreated patients. This analysis was originally presented at the Institute on Psychiatric Services of the American Psychiatric Association 2002 annual meeting (October).

2. What is AstraZeneca doing to monitor the link between diabetes and use of SEROQUEL?

The safety of our products always is our highest priority. AstraZeneca maintains a robust clinical safety database and has fulfilled every compliance requirement, including reporting obligations to all regulatory authorities. Through our global safety database we continuously monitor all our products, including SEROQUEL, and review this information to update Health Authorities accordingly. Our physicians and scientists also stay abreast of developments in the scientific literature that may have implications for our products, including SEROQUEL.

3. Obesity can be a risk factor for diabetes. What effect does SEROQUEL have on body weight?

As with other atypical antipsychotics, some weight gain has been reported with SEROQUEL. The weight gain profile for SEROQUEL compares favorably with other atypical drugs in this class of antipsychotics.

In addition, Seroquel has a very favorable side effect profile. Regardless of dose, patients taking SEROQUEL experienced side effects no different than placebo in a troubling area -- extrapyramidal symptoms (restlessness and movement disorders) -- and in elevation of serum prolactin levels.

4. Do the other atypicals cause weight gain?

There have been reports in the medical literature of weight gain associated with other atypicals.

5. Do you have specific data to back up your claim that SEROQUEL does not cause or exacerbate diabetes?

AstraZeneca believes that the available data do not establish a causal link between SEROQUEL and diabetes. Since its approval in 1997, there have been more than 6.1 million patient exposures to SEROQUEL worldwide. A retrospective analysis of 17,000 patients with psychosis revealed that those treated with SEROQUEL had estimated odds of receiving treatment for type 2 diabetes that were no more than those of untreated patients. This analysis was originally presented at the Institute on Psychiatric Services of the American Psychiatric Association 2002 annual meeting (October).

Label Change

6. If AZ maintains that there is no causal effect between SEROQUEL and diabetes, why has the company agreed to change the drug's label?

While AstraZeneca believes that the available data do not establish a causal link between SEROQUEL and diabetes, AstraZeneca also feels that the labeling changes requested by the FDA for all atypical antipsychotics may serve as a helpful reminder to prescribing physicians that certain patients under their care may be especially susceptible to hyperglycemia and diabetes due to their underlying disease and related factors.

7. What does the new label state about diabetes?

The current SEROQUEL PI lists diabetes mellitus and hyperglycemia in the "Adverse Events" Section. The FDA is requesting that the PI for all atypical antipsychotics, including SEROQUEL, now include a statement under "Warnings about Hyperglycemia and Diabetes Mellitus."

IF PRESSED: The warning will inform patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics to be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment.

It is important to note that the FDA acknowledged that the relationship between atypical antipsychotic medications and diabetes mellitus adverse events is not fully understood and requires further research. The agency has noted in particular that the "assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in

patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population."

AstraZeneca believes that the available data do not establish a causal link between diabetes and SEROQUEL.

8. Isn't changing the label basically admission that AZ knows there is some sort of problem?

No. While AstraZeneca believes that the available data do not establish a causal link between SEROQUEL and diabetes, AstraZeneca also feels that the labeling changes requested by the FDA for all atypical antipsychotics may serve as a helpful reminder to prescribing physicians that certain patients under their care may be especially susceptible to hyperglycemia and diabetes due to their underlying disease and related factors.

IMPORTANT TO NOTE: The Q&A below will be active once the HCP letter is sent. As of this date, it has not.

Did AstraZeneca recently send a Dear Healthcare Provider letter to physicians regarding diabetes? What was the reason behind this?

AstraZeneca recently sent a Dear Healthcare Provider letter to inform providers of important labeling changes regarding SEROQUEL. The FDA asked all manufacturers of atypical antipsychotic medications, including AstraZeneca, to add additional information regarding the detection and management of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL.

Litigation

9. Has AstraZeneca been threatened with lawsuits for SEROQUEL regarding its link to diabetes?

AstraZeneca is defending a putative class action lawsuit filed in Florida in September 2003 involving SEROQUEL and diabetes. Also, a lawsuit against Eli Lilly and AstraZeneca recently has been filed in Virginia involving Zyprexa and SEROQUEL. The company does not comment on pending litigation. However, since its approval in 1997, there have been more than 6.1 million patient exposures to SEROQUEL worldwide. AstraZeneca believes that the available data do not establish a causal link between SEROQUEL and diabetes.

Pancreatitis

10. Is there a link between SEROQUEL and pancreatitis?

SEROQUEL is not casually associated with pancreatitis, a position supported by clinical trials and continuous post marketing experience. The safety of our products always is our highest priority. The company continuously monitors all of its products, including

SEROQUEL, to ensure any potential safety issues are identified and managed in a way that promotes their continued safe use.

11. What does AstraZeneca think about the recent study that appeared in *Pharmacotherapy* regarding atypicals and the incidence of pancreatitis?

AstraZeneca is aware of study results published in the September issue of *Pharmacotherapy*, which showed there may be a link between some of the newer antipsychotic drugs prescribed for schizophrenia, such as Zyprexa, Risperdal and Clozaril, and an inflammation of the pancreas, known as pancreatitis. However, SEROQUEL, an atypical antipsychotic indicated for the treatment of schizophrenia and bipolar mania was not included in this study, therefore we cannot comment further.

Wall Street Journal (WSJ) Article of August 22, 2003 and Cunningham/ US Veteran's Administration (VA) Study

12. Why does the WSJ article contain incomplete and therefore misleading information regarding the results of the VA study?

The August 22 WSJ article was based on an abstract of preliminary and incomplete findings from the study. Where the WSJ article reported that SEROQUEL patients had the highest association with diabetes among the three atypical antipsychotics studied, the complete findings presented at the International Society of Pharmacoepidemiology on August 24, 2003 showed otherwise. Specifically, the presentation of the complete findings state that the risk of developing diabetes in SEROQUEL-treated patients was not statistically different than typical antipsychotics while the other atypicals that were studied (olanzapine and risperidone) were associated with higher risks.

13. Why were the findings presented in the abstract different from the completed study findings presented at the meeting?

Among other things, the complete study findings considered an extended period of time and additional data (e.g., inpatient data). In the final analysis, the investigators were

better able to exclude patients previously exposed to atypical antipsychotics or who were predisposed to diabetes. When the patient population was defined in this way, the diabetes hazard rates decreased significantly from what had been reported in the abstract.

14. What were the sample sizes used in the study?

Including in-patient and outpatient data, the cohort consisted of 877 quetiapine patients, 5981 olanzapine patients, and 5901 risperidone patients.

15. What were the limitations of the study design?

There are several limitations of this type of study. They include, but are not limited to:

- Because patients were treated in a naturalistic clinical setting, they were not assigned randomly but by clinical judgment. Because this judgment may have included avoiding medications that were associated with diabetes or risk factors for diabetes (e.g., weight), SEROQUEL may have been systematically selected for those patients with the greatest diabetes risk. This meant that there was potential for introducing systematic bias, and putting SEROQUEL at a disadvantage.
- To avoid this systematic bias, investigators must be able to control for significant diabetes risk factors. Because of the nature of the databases that were used, the investigators were unable to control for some important diabetes risk factors, including weight, family history, and diet.

Because of this, the authors cannot exclude the possibility that any findings from the study were due to the nature of the patient selection and not to the medications. **The available data, including this study, do not establish a causal link between SEROQUEL and diabetes.**

16. What is the relevance of the NY Times article? How does it differ from the WSJ piece?

The NY Times article reported on the complete study findings presented at the meeting, which showed that the risk of developing diabetes in SEROQUEL-treated patients was not statistically different than patients treated with typicals.

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