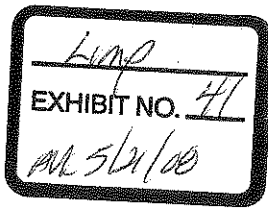
From: Melville, Margaret G
Sent: Sunday, October 20, 2002 9:17 PM
To: Griffiths, Jonathan; Limp, Gerald L; Bradley, Kathryn; Wilkie, Alison M; Leong, Ronald
Subject: Request for information on diabetic events



Attachments: risperidol.html; zyprexa.html; Seroquel/Diabetes/ Japan

Dear All,

The product manager in New Zealand has provided us with the below information regarding Lilly's activities in New Zealand. We have been asked to provide some information in order to assist in a response. The response has been requested to be provided by October 25.

Can I ask for your assistance? I have added initials to the below in hopes you can be actioned to help with this. Can we meet the timings that have been requested?

With regard to Bullet 2, Gerald, and Kathryn, I have a response that Gerald had prepared earlier. Has anything changed to your knowledge?

As you know diabetes mellitus is listed in the US PI. This was done at the time of approval. On 1 May 2000, the FDA did send us a letter requesting information pertaining to this broad issue. Informally, they informed us that they were considering sending a letter to Lilly requesting a higher level of labeling precaution for diabetes for Zyprexa, but first wanted to see whether the other drugs in this atypical class also had a similar problem (might justify a class label precaution, in other words), and so, we assume Janssen received a similar letter.

Specifically, the FDA's letter requested more extensive safety information regarding new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis. AZ sent a response dated 31 August 2000. No labelling changes have been required.

Zyprexa has the following in their labeling in the US in the AE section (I have enclosed it as well):

Weight Gain --In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Endocrine System -- Infrequent: diabetes mellitus; Rare: diabetic acidosis and goiter.
Metabolic and Nutritional Disorders -- Infrequent: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, and water intoxication; Rare: gout, hyperkalemia, hypernatremia, hypoproteinemia, and ketosis.

Risperadol has the following in their labeling in the US in the AE section (the PI is enclosed):

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Alison, with regard to the last two bullets, we have just done a cumulative review of all glucose related events, and written a report, for filing to MHLW in Japan. All DKA cases are reviewed, starting on page 31, and narratives are provided. I attach this, thinking that it will suffice for bullet three. Can you confirm? Can you also confirm what is meant by the fourth bullet "an overview of similar Lilly activity internationally"?

Thanks All,

Best Regards,

Meg

Eli Lilly in New Zealand have developed sales material claiming that Zyprexa is no different to other antipsychotics in terms of diabetic events, and reference this claim to 2 Eli Lilly sponsored posters by Allison and Cavazzoni. We have submitted a formal complaint to our local industry association regulating committee, with documented evidence of increased risk of diabetes with Zyprexa compared to other antipsychotics. This evidence includes the recent Koro paper from the BMJ, Giofrancesco's APA poster and numerous smaller studies. We have also included details of the change of label of Zyprexa in Japan.

Could you advise:

details of label changes in the UK for Zyprexa and Seroquel JG
an up-date of possible label changes by the FDA for atypicals GL/KB
more specific details regarding the death reported in Japan from ketoacidosis with quetiapine MGM
an overview of similar Lilly activity internationally ??

We have a committee hearing in 2 weeks, so we wish to gather as much information as possible to support our arguement that the risk of developing diabetes is greater with Zyprexa than "other" antipsychotics.

Margaret (Meg) Melville
Seroquel Global Regulatory Affairs Director
((302) 886-2118 or 1(800) 456-3669 X 62118
mobile REDACTED
fax (302) 886-1400
: margaret.melville@astrazeneca

From: Warner, Linda (Safety)
Sent: Tuesday, October 15, 2002 4:19 PM
To: Melville, Margaret G
Cc: Trumble, Sharon M; Leong, Ronald
Subject: Seroquel/Diabetes/ Japan

Attachments: Assessment of Diabetes in Patients Treated with SeroquelF2.doc

Folks,
Here is a copy of the Japan response Diabetes document with the number 93 in both the summary page and section 5 post marketing. We had received 92 reports coded for diabetes related AE and an additional report was reveiwed because it referred to a "possible" diabetes related term in the narrative although there was no preferred term included. I realize this was not clear from the two numbers, so i made both numbers 93 to make it simple.

Linda Warner MS RN
Safety Surveillance TA Team Leader
Drug Safety, AstraZeneca, FOC W2-659
Linda.Warner2@AstraZeneca.com
302-885-9078

AstraZeneca

Assessment of Diabetes in Patients Treated with Seroquel	
Drug Substance	quetiapine fumarate
Document No.	
Edition No.	
Date	11 October 2002
Amends	

Assessment of Diabetes in Patients Treated with Seroquel® (quetiapine fumarate): Response to Japanese MHLW

Period covered: Cumulative through 02 October 2002

TABLE OF CONTENTS PAGE

1. INTRODUCTION

The purpose of this document is to assess whether there is a causal association between treatment with Seroquel (quetiapine fumarate; quetiapine) and diabetes. The possibility of such an association was raised in a communication from the MHLW agency to AstraZeneca, based on twelve Japanese diabetes mellitus or hyperglycemia reports for Seroquel. The MHLW requested that the 12 reports as well an any other reports related to diabetes for all other countries be reviewed by AstraZeneca. All reports of diabetes related adverse events in patients receiving Seroquel, that were received from Japan, as well as any other country, are reviewed in this document. A review of AstraZeneca's available relevant preclinical, clinical trial, and postmarketing spontaneous safety data was performed. In addition, the scientific/medical literature was reviewed for relevant articles. A summary of the assessment is presented in section two of this document. The preclinical, clinical trial and post-marketing surveillance data are presented and discussed in full in sections three, four and five of this document, respectively. The literature review and an overall conclusion is presented in section six and seven, respectively.

2. SUMMARY

- There is no evidence from preclinical data that Seroquel treatment in man may be associated with diabetes. The only salient observations are small changes in glucagon secreting cells in a 1-year rat study with quetiapine. No such changes were observed after administration of quetiapine at the same dose levels for two years in another rat study. Further, no such changes were observed in any of the other species tested in the preclinical program, and no changes in serum glucose levels or pathology indicative of a diabetic condition were observed throughout the preclinical toxicology program. Thus the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in man.

- Adverse event data from over 3000 patients exposed to Seroquel during clinical trials has shown that the incidence of adverse events possibly associated with disturbances in glucose regulation is low, and does not increase as duration of exposure to Seroquel increases. No cases of diabetic ketoacidosis or hyperosmolar coma were reported, and only five cases (0.1%) of diabetes mellitus were reported (all of which were considered by the investigator to be unrelated to trial treatment).

- Obesity can be a risk factor for diabetes. Only one of the 67 patients with weight gain in the clinical trial program also had diabetes mellitus recorded as an adverse event. However, this patient had diabetes at baseline (which was being treated). The latest analyses (from Trial 5077IL/0051) have shown that Seroquel has a minimal effect on weight gain in the long-term, at all doses.

- Plasma glucose data from clinical trials has shown that hyperglycemia (random glucose value ≥ 200 mg/dl) was observed in a small number of patients treated with Seroquel, but was not sustained, extreme, or associated with any symptoms. Further, the incidence of hyperglycemia did not increase as the duration of exposure to Seroquel increased. In addition, there were no statistically significant differences between Seroquel and placebo in the mean changes from baseline to endpoint in plasma glucose levels.

- All the reports received from Japan are either confounded, or have alternative explanations or a negative dechallenge, or had documentation of hyperglycaemia or poor diabetes control prior to receiving Seroquel. These reports provide insufficient information to establish a causal relationship between Seroquel and diabetes, hyperglycaemia, exacerbation of diabetes, or diabetic ketoacidosis.

- Worldwide (including Japan) postmarketing reports comprise 93 cases of new-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, diabetic ketoacidosis or hyperglycaemia. However, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. This position is supported by the literature where the incidence of diabetes mellitus in the schizophrenic population is noted to exceed that in the general population, even prior to the introduction of atypical antipsychotic medications (Dixon et al 2000).

3. REVIEW OF PRECLINICAL DATA

AstraZeneca has completed a comprehensive review of all the preclinical data for evidence of an association between quetiapine treatment and disturbances in glucose metabolism.

3.1 Salient Observations

Hyperplasia of small glucagon secreting cells (alpha cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day dose groups following administration of quetiapine for 12 months to rats (TFR/1626). The changes observed were minimal in severity and were not observed after administration for two years at the same dose levels in another rat study (TCR/1624).

No such changes were observed in the pancreatic islets of mice, dogs or primates during single-or multiple- dose studies (of up to 12 months duration) with quetiapine. In addition, no consistent changes in blood glucose levels occurred during any toxicology study in any species. Further, throughout all the extensive preclinical toxicity studies, there was no degenerative pathology that would reflect the induction of a diabetic state.

3.2 Discussion

A functional change in pancreatic islets might be an expected consequence of administration of a dopamine receptor antagonist that increases circulating prolactin. The lactogenic hormones can modulate pancreatic islet beta-cell function (Landgraf et al 1977, Nielsen JH et al 1982, Michaels RL et al 1987); prolactin stimulates an increase in islet cell protein synthesis leading to an increased secretion of insulin (Markoff et al 1990). Conversely, dopamine agonists decrease the glucose-stimulated release of insulin from beta-cells (Morricone et al 1990, Cavaziel et al 1981). The major physiological importance of glucagon (from alpha-cells) relates to its involvement in metabolic control, where its actions generally oppose that of insulin (Unger et al 1981). Because of its close interrelationship with insulin, many of the drugs that affect beta-cells and insulin also produce effects on alpha cells and glucagon (Woodman 1997).

The above observations in the rat study, together with the literature reports of the effects of dopamine antagonists, would suggest that there is a possibility of quetiapine affecting islet cell homeostasis. However, no such findings were observed in any of the other species in the toxicology program, and no glucose changes or pathology indicative of a diabetic condition were observed throughout the preclinical program. Thus the hyperplasia of glucagon secreting cells observed in the single rat study appears to be of little or no pathologic consequence and thus does not have the potential for clinical significance.

3.3 Conclusion

A review of all the preclinical data has confirmed that the only salient observations are the small changes in glucagon secreting cells in a one year rat study with quetiapine. This observation is considered to be of minimal pathological significance and would not be expected to have any clinical significance in man. Overall, it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

4. REVIEW OF CLINICAL DATA

AstraZeneca has thoroughly reviewed adverse event data and plasma glucose data from the clinical trials database for evidence of an association between Seroquel treatment and disturbances in glucose metabolism.

4.1 Source material

4.1.1 Adverse event data

4.1.1.1 Incidence of adverse events possibly associated with disturbances in glucose metabolism

AstraZeneca has analyzed the incidence of adverse events possibly associated with disturbances in glucose metabolism in the integrated safety database of the original registration dossier. In this database, adverse events were categorised using an in-house dictionary based on the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). For the purpose of this review, a list of COSTART terms for adverse events that could possibly be associated with disturbances in glucose metabolism has been identified, and are as follows:

> *thirst, polyuria, urinary frequency, weight gain, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, hyperosmolar coma*

A summary of exposure to treatment in the integrated safety database prepared for the original registration dossier is presented in Table 1.

Table 1 **Summary of treatment exposure in the Mutual Recognition integrated safety database**

Pools by trial design	Treatment group and number of patients				
	Seroquel	**Placebo**	**Haloperidol**	**Chlorpromazine**	**Risperidone**
Phase 1	553	0	0	0	0
Controlled Phase II/III	2185	206	320	230	208
Short-term (≤ 6 weeks duration)	1925	206	279	230	208
Long-term (> 6 weeks duration)	260	0	41	0	0
Uncontrolled	1640	0	0	0	0
New exposures	768	0	0	0	0
Patients already counted under previous headings[a]	872	0	0	0	0
All trials[b]	**3506**	**206**	**320**	**230**	**208**

[a]Previously took part in controlled Phase II/III trials
[b]Only includes the new exposures in the uncontrolled trials

In order to observe the effect of an increased duration of exposure to Seroquel on the incidence of the adverse events listed above, the adverse data in this report have been divided into the following trial pools:

- Phase I trials (Seroquel; N=553)
- Short-term controlled Phase II/III trials (≤ 6 weeks duration: Seroquel; N=1925, placebo; N=206, haloperidol; N=279, chlorpromazine; N=230, risperidone; N=208)
- Long-term controlled Phase II/III trials (> 6 weeks duration: Seroquel; N =260, haloperidol; N=41)
- Uncontrolled Phase II/III trials (Seroquel; N=1640)

As the time-on-study in each treatment group will have varied, overall *incidence density* rates, as well as normal cumulative incidence rates, are presented in this report. (Incidence density is defined as the total number of patients with an event, divided by the total patient year exposure).

4.1.1.2 Long-term effect of Seroquel on weight

As obesity can be a risk factor for diabetes, the effect of Seroquel on weight change in the long-term has been analysed in some detail. The analysis is from Trial 5077IL/0051, which

consisted of open-label extensions of 6 randomised, comparator IIIb trials of Seroquel monotherapy (Trials 5077IL/0049, IL/0050, IL/0052, IL/0053, IL/0054 and IL/0072). (Trial 5077IL/0051 is not part of the integrated safety database prepared for the original registration dossier). All the patients in Trial 5077IL/0051 had completed at least 4 weeks of Seroquel treatment in 1 of 6 Phase IIIb clinical trials before entering the trial.

To assess the long-term effects of Seroquel on weight gain, a cohort of schizophrenic patients who provided weight data at least 6 months after the start of monotherapy Seroquel treatment was selected (n=178). The change from baseline to their final weight on Seroquel treatment was examined. The mean duration of treatment was 18.6 months. The mean dose of Seroquel that the patients received was 473 mg/day. All the patients were flexibly dosed with Seroquel up to 800 mg/day during the open-label extension phases. In order to analyze the effect of baseline status on weight change with Seroquel, patients were stratified into the following 5 categories according to their body mass index (BMI) at baseline: <18 kg, <25 kg, <30 kg, <35 kg and ≥ 35 kg.

The effect of dose on weight change with Seroquel has also been assessed. Three Seroquel dose groups were selected: <300 mg, 300 to 500 mg and >500 mg. For each dose group, the absolute mean weight data were obtained from the same cohort of patients at baseline and at endpoint. Endpoint was defined as the final weight value that was taken for each patient. Dose groups were calculated using the modal dose value for the time period when the last weight value was recorded.

4.1.2 Plasma glucose data

Plasma glucose data were collected in the following trials in the Seroquel Mutual Recognition integrated database:

- three short-term placebo controlled trials (204636/0008, 5077IL/0004, 5077IL/0006) (Seroquel; N=230, placebo; N=143)
- one short-term comparator controlled trial (204636/0007) (Seroquel; N=93, chlorpromazine; N=92)
- one long-term comparator controlled trial (5077IL/0015) (Seroquel N=170, haloperidol; N=35)

(N is the number of patients with both baseline and end of treatment glucose data).

4.1.2.1 Mean change from baseline in plasma glucose levels

Mean changes from baseline to end of treatment in plasma glucose levels have been presented for the 3 trial pools indicated in Section 4.1.2. To observe any statistically significant differences between the treatment groups in each trial pool, the data were analyzed using analysis of covariance, including the baseline score, treatment, center and center-by-treatment interaction as factors. Differences between the treatments were estimated and 95% confidence intervals and p values have been presented.

4.1.2.2 Patients meeting criteria for a markedly abnormal plasma glucose level

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1998) have defined the diagnostic criteria for diabetes as follows: symptoms of diabetes plus a casual plasma glucose concentration ≥ 200 mg/dl; or a fasting blood glucose level equal to or > 126 mg/dl or a 2-hour blood glucose level ≥ 200 mg/dl during an oral glucose tolerance test (Diabetes Care 1997; 20:1183–1197).

In the Seroquel clinical trials, the investigators were not instructed when to take plasma samples for assessment of glucose levels, and thus the glucose values obtained were *random* values. Therefore, based on the criteria defined by the Expert Committee above, AstraZeneca has defined a markedly abnormal plasma glucose concentration as ≥ 200 mg/dl, at any time.

Number of patients with a markedly abnormal plasma glucose level

The number of patients with a plasma glucose concentration of ≥ 200 mg/dl at any time will be summarized by baseline glucose level, as follows:

- patients with a baseline glucose < 200 mg/dl
- patients with a baseline glucose ≥ 200 mg/dl
- all patients, irrespective of the baseline value

To observe the effect of an increased duration of exposure to trial treatment on the number of patients with a markedly high glucose level, the above data will be summarised in two trial pools: short-term trials and long-term trials. As with the adverse event data, in order to adjust for time-on-study, overall incidence density rates, as well as the normal cumulative incidence rates, will be presented for the proportion of patients with a plasma glucose level ≥ 200 mg/dl at any time.

Profiles of patients with a markedly abnormal plasma glucose level

In order to analyze plasma glucose values over the course of treatment, and to obtain details on whether the patients had any symptoms of diabetes, detailed profiles of each patient with a plasma glucose level ≥ 200 mg/dl at any time have been obtained and assessed in this report.

4.2 Results

4.2.1 Adverse event data

4.2.1.1 Incidence all adverse events that could possibly be associated with disturbances in glucose metabolism

Phase I trials

The number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism across the Phase I trials are presented in Table 2.

Table 2 **Number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism in the Phase I trials**

COSTART term[a]	Number (%) of patients
	Seroquel (N=553)
Thirst	0
Polyuria	2 (0.4)
Urinary frequency	3 (0.5)
Weight gain[b]	1 (0.2)
Hyperglycemia	3 (0.5)
Diabetes mellitus	0
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**9 (1.6)**
Total number of events	**9**
Total patient year exposure[c]	**22.6**
Incidence density[d]	**0.4**

[a]Each patient may have more than 1 adverse event
[b]Any weight gain event, irrespective of the magnitude of the gain
[c]Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365. Note that exposure data was only available for 549 patients.
[d]Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Nine patients (1.6%) had adverse events possibly associated with disturbances in glucose metabolism in the Phase I trials. No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. Urinary frequency and hyperglycemia were the most commonly reported events in these trials. None of the events in Table 2 were considered serious by the Investigator, or led to withdrawal from treatment.

CONTROLLED PHASE II/III TRIALS

Short-term trials

The number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism across the short-term controlled Phase II/III trials (≤ 6 weeks duration) is presented in Table 3.

Table 3 **Number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism in the short-term controlled Phase II/III trials**

COSTART term[a]	Number (%) patients				
	Seroquel (N=1925)	Placebo (N=206)	Haloperidol (N-279)	Chlorpromazine (N=230)	Risperidone (N=208)
Thirst	4 (0.2)	0	0	0	1 (0.5)
Polyuria	2 (0.1)	0	0	1 (1.0)	0
Urinary frequency	2 (0.1)	0	1 (0.4)	0	2 (1.0)
Weight gain[b]	25 (1.3)	0	3 (1.1)	2 (0.9)	3 (1.4)
Hyperglycemia	0	0	0	0	
Diabetes mellitus	0	0	0	0	
Diabetic ketoacidosis	0	0	0	0	
Hyperosmolar coma	0	0	0	0	
Total number of patient with events	**30 (1.6)**	**0**	**4 (1.4)**	**3 (1.3)**	**6 (2.9)**
Total number of events	**33**	**0**	**4**	**3**	**6**
Total patient year exposure[c]	**171.3**	**14.6**	**24.8**	**29.0**	**32.4**
Incidence density[d]	**0.2**	**0**	**0.2**	**0.1**	**0.2**

[a]Each patient may have more than 1 adverse event
[b]Any weight gain event, irrespective of the magnitude of the gain
[c]Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d]Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Thirty patients (1.6 %) treated with Seroquel had adverse events possibly associated with disturbances in glucose metabolism in the short-term controlled trials. The incidence density was 0.2, which is similar to that observed in the comparator groups.

Three patients each had two events in the Seroquel group; one patient had thirst and weight gain, and two patients had thirst and polyuria.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported.

The most frequently reported event in patients treated with Seroquel was weight gain (25 patients, 1.3%); this occurred at a similar incidence as that in the haloperidol (1.1%) and risperidone (1.4%) groups. (Note: the adverse event of 'weight gain' refers to *any* weight gain, irrespective of the magnitude of the gain).

One patient was withdrawn from treatment due to weight gain (5077IL/0012/0007/0708). The Investigator did not considered this event to be serious. A review of this patient's details

revealed that, in addition to weight gain (2.0 kg over two weeks), this patient also withdrew for reasons of somnolence and abdominal distension.

Apart from the one case of weight gain discussed above, none of the other events in Table 3 led to a patient being withdrawn from treatment, or were considered serious by the investigator.

Long-term trials

The number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism across the long-term controlled Phase II/III trials (> 6 weeks duration) is presented in Table 4.

Table 4 **Number (%) of patient with adverse events possibly associated with disturbances in glucose metabolism in the long-term-controlled Phase II/III trials**

COSTART term[a]	Number (%) of patients	
	Seroquel (N=260)	Haloperidol (N=41)
Thirst	1 (0.3)	0
Polyuria	0	0
Urinary frequency	0	0
Weight gain[b]	12 (4.6)	0
Hyperglycemia	0	0
Diabetes mellitus	0	0
Diabetic ketoacidosis	0	0
Hyperosmolar coma	0	0
Total number of patient with events	**13 (5.0)**	**0**
Total number of events	**13**	**0**
Total patient year exposure[c]	**84.5**	**17.8**
Incidence density[d]	**0.2**	**0**

[a]Each patient may have more than 1 adverse event
[b]Any weight gain event, irrespective of the magnitude of the gain
[c]Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d]Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Thirteen patients (5.0%) treated with Seroquel had adverse events possibly associated with disturbances in glucose metabolism in the long-term controlled trials. The incidence density was 0.2, which is the same as that observed in the short-term trials (Table 3), indicating that

the incidence of adverse events possibly associated with disturbances in glucose metabolism does not increase as duration of exposure to Seroquel increases.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported in either treatment group. Weight gain was the most frequently reported event in the Seroquel group.

None of the events in Table 4 were considered serious by the investigator, or led to withdrawal from treatment.

Uncontrolled Phase II/III trials

The number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism across the uncontrolled Phase II/III trials are presented in Table 5

Table 5 Number (%) of patients with adverse events possibly associated with disturbances in glucose metabolism in the Phase II/III trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=1640)
Thirst	2 (0.1)
Polyuria	1 (0.1)
Urinary frequency	7 (0.4)
Weight gain[b]	48 (2.9)
Hyperglycemia	8 (0.5)
Diabetes mellitus	5 (0.3)
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**66 (4.0)**
Total number of events	**71**
Total patient year exposure[c]	**894.4**
Incidence density[d]	**0.1**

[a]Each patient may have more than 1 adverse event
[b]Any weight gain event, irrespective of the magnitude of the gain
[c]Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365. Note that exposure data was only available for 549 patients.
[d]Incidence density is defined as the total number of patients with events divided by the total patient year exposure

In total, 4.0 % of patients had adverse events possibly associated with disturbances in glucose regulation in the uncontrolled trials.

Five patients each had two events: one patient had hyperglycemia and urinary frequency, one patient had thirst and polyuria, one patient had diabetes mellitus and weight gain, one patient

had hyperglycemia and weight gain and one patient had diabetes mellitus and urinary frequency. Weight gain was the most frequently reported event in these trials.

No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Five cases (0.3%) of diabetes mellitus were reported. In two cases (5077IL/0012/0046/4603 and 5077IL/0015/0005/0509), the patients had a history of diabetes. In a third case (5077IL/0014/0036/3605), the patient is reported to have 'recovered' from the diabetes whilst on Seroquel treatment following treatment with glibenclamide. None of the five cases of diabetes mellitus were considered by the investigator to be related to trial therapy. In addition, none of the five cases were considered by the investigator to be serious, or led to withdrawal of treatment.

Three patients were withdrawn from treatment in this trial pool; all three were withdrawn due to hyperglycemia. One of the three patients (5077IL/0048/0003/0310) died of myocardial infarction. Hyperglycemia, as well as severe pancreatitis, dehydration, pneumonia, hyponatremia and hyperkalemia, were all noted in concurrence with the myocardial infarction. The patient in question was 77 years old and had a history of borderline diabetes mellitus. In the remaining two cases, both patients had significant confounding factors: one patient (5077IL/0012/0093/9304) had a history of hyperglycemia and diabetes and the other patient (5077IL/0013/0001/0109) had a history of borderline elevated glucose levels. In all three cases, the investigator considered the hyperglycemia events to be serious, but unrelated to treatment with Seroquel.

Apart from the three events of hyperglycemia discussed above, none of the other events in Table 5 were considered to be serious by the investigator, or led to withdrawal from treatment.

4.2.1.2 Long-term effect of Seroquel on weight

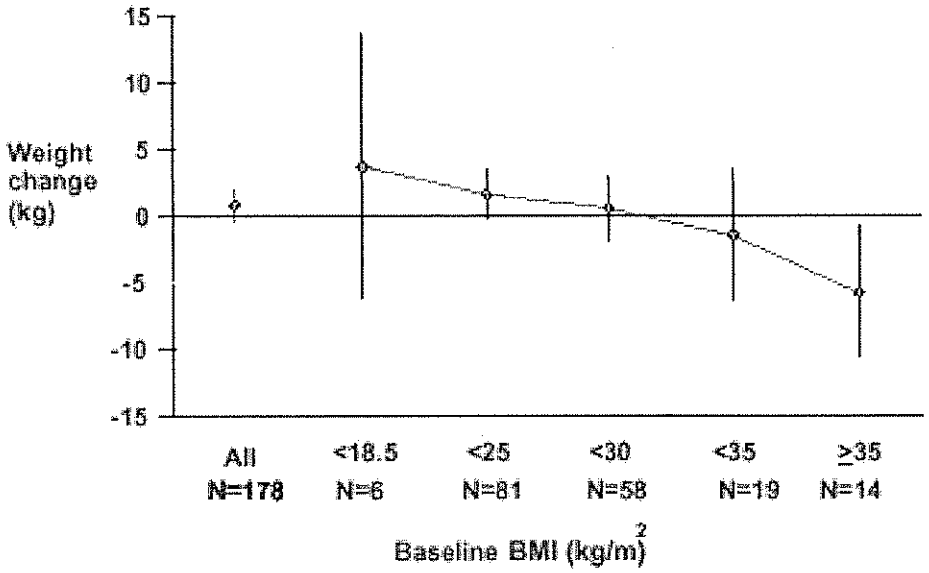
The results of the analysis of the long-term effect of Seroquel on weight (Trial 5077IL/0051) is presented in Table 6 (mean weight change by baseline BMI; see also Figure 1) and Table 7 (mean weight change by Seroquel ; see also Figure 2).

Table 6 Long-term effect of Seroquel on weight by baseline BMI

Baseline BMI (kg/m^2)	N	Mean weight change (kg)	LCL	UCL
All	178	0.412	-0.918	1.742
<18.5	6	3.750	-6.277	13.777
<25	81	1.605	-0.212	3.422
<30	58	0.528	-1.891	2.946
<35	19	-1.532	-6.480	3.417
≥35	14	-5.757	-10.67	-0.840

BMI Body mass index
N Number of patients included in the analysis
LCL Lower confidence limit
UCL Upper confidence limit

Figure 1 Long-term effect of Seroquel on weight (mean, 95% CIs)



Minimal weight gain was seen in the group as a whole. Seroquel monotherapy had a minimal effect on weight across all the baseline BMI categories (overall mean weight change of 0.412 kg , n=178, 95% CI includes 0) except for the most severely obese group (BMI of 35 or more), in whom the mean weight decreased.

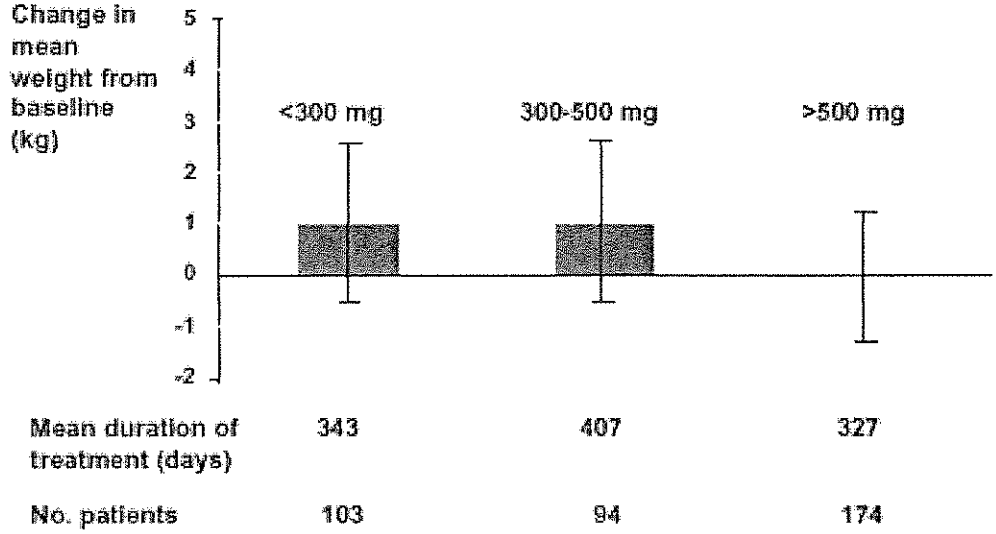
Table 7 Effect of Seroquel dose on weight

Weight (kg)	Dose (mg/day)		
	≤300 (n=103)	>300-500 (n = 94)	>500 (n= 174)
Baseline			
Mean	75.12	72.05	75.38
Median	71.50	70.25	72.75
95% confidence interval	71.6, 78.6	69.2, 74.9	73.1, 77.6
Endpoint			
Mean	76.12	73.11	75.32
Median	72.30	72.25	73.00
95% confidence interval	72.4, 79.9	69.9, 76.3	73.0, 77.6
Change from baseline			
Mean	1.01	1.06	-0.06
Median	0.00	-0.25	0.00

Table 7 Effect of Seroquel dose on weight

Weight (kg)	Dose (mg/day)		
	≤300 (n=103)	>300-500 (n = 94)	>500 (n= 174)
95% confidence interval	-0.5, 2.5	-0.5, 2.6	-1.3, 1.2

Figure 2 Effect of dose of Seroquel on weight change



The vertical lines in Figure 2 show the 95% confidence intervals. The 95% confidence intervals include zero for all three dose groups, indicating that the effect of Seroquel on patient weight was minimal across the dose range.

Table 8 **Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term placebo-controlled trials**

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
Seroquel	230	3.60	1.52					
Placebo	143	-0.26	1.93					
Seroquel versus placebo				3.87	2.46	-0.97	8.71	0.1173

LS Least square mean, SE Standard error, Diff Difference between treatments, LCL Lower 95% confidence limit, UCL Upper 95% confidence limit, N is based on the number of patients with both baseline and end of treatment glucose data

Table 9 **Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term comparator-controlled trials**

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
Seroquel	93	-1.30	1.98					
Chlorpromazine	92	-1.20	1.99					
Seroquel versus chlorpromazine				-0.10	2.81	-5.64	5.44	0.9721

LS Least square mean, SE Standard error, Diff Difference between treatments, LCL Lower 95% confidence limit, UCL Upper 95% confidence limit, N is based on the number of patients with both baseline and end of treatment glucose data

Table 10 **Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term trials**

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
Seroquel	170	4.53	2.57					
Haloperidol	35	4.01	5.68					
Seroquel versus haloperidol				0.52	6.24	-11.79	12/83	0.93333

LS Least square mean, SE Standard error, Diff Difference between treatments, LCL Lower 95% confidence limit, UCL Upper 95% confidence limit, N is based on the number of patients with both baseline and end of treatment glucose data

Table 11 **Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term open, uncontrolled trial in elderly subjects**

Treatment	N	Mean change from baseline (mg/dL)	
		Mean	Std. Dev.
Seroquel	153	9.53	51.74

From Trial 5077IL/ 0048; N is based on the number of patients with both baseline and end of treatment glucose data

The differences between the treatment groups within each trial pool were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine or Seroquel versus haloperidol).

4.2.1.3 Patients meeting the criteria for a markedly abnormal plasma glucose level

Number of patients meeting criteria for a markedly abnormal plasma glucose level

The number of patients with a plasma glucose level ≥ 200 mg/dl at any time post baseline has been summarized in Table 12 (short-term trials), Table 13 (long-term trials) and Table 14 (long-term trial in elderly subjects), according to the baseline glucose level.

Table 12 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in short-term trials[a]

Baseline glucose level	Treatment group		
	Seroquel (N=323)	Placebo (N=143)	Chlorpromazine (N=92)
Number of patients with baseline glucose < 200 mg/dL	322	142	92
Number (%[b]) of patient with glucose ≥ 200 mg/dL post-baseline	10 (3.1)	1 (0.7)	0
Number of patients with baseline glucose >200 mg/dL	1	1	0
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	1 (100%)	0 (0)	0
All patients, irrespective of baseline glucose value	**323**	**143**	**92**
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**11 (3.4)**	**1 (0.7)**	**0**
Total patient year exposure[c]	**28.1**	**10.6**	**8.8**
Incidence density[d]	**0.4**	**0.1**	**0**

[a]from Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006 [b]% uses total number of patients in baseline sub-group as a denominator
[c]Total patient year exposure is defined a the sum of days on treatment for each patient, divided by 365
[d]Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure
N is the number of patients with both baseline and end of treatment glucose data

Table 13 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	Seroquel (N=170)	Haloperidol (N=35)
Number of patients with baseline glucose < 200 mg/dL	167	32
Number (%[b]) of patient with glucose ≥ 200 mg/dL post-baseline	2 (1.2)	1 (3.1)
Number of patients with baseline glucose >200 mg/dL	3	3
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	3 (100)	2 (66.7)
All patients, irrespective of baseline glucose value	**170**	**35**

Table 13 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	Seroquel (N=170)	Haloperidol (N=35)
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**5 (2.9)**	**3 (8.6)**
Total patient year exposure[c]	**68.1**	**16.4**
Incidence density[d]	**0.1**	**0.2**

[a]from Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0-006 [b]% uses total number of patients in baseline sub-group as a denominator
[c]Total patient year exposure is defined a the sum of days on treatment for each patient, divided by 365
[d]Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure
N is the number of patients with both baseline and end of treatment glucose data

Table 14 Number (%) of patients with glucose ≥ 200 mg/dL (random values) in long-term trials in elderly subjects[a]

Baseline glucose level	Seroquel
Number of patients with baseline glucose < 200 mg/dL	148
Number (%[b]) of patient with glucose ≥ 200 mg/dL post-baseline	2 (1.4)
Number of patients with baseline glucose >200 mg/dL	5
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	5 (100)
All patients, irrespective of baseline glucose value	**163**
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**8[c] (4.9)**
Total patient year exposure[d]	**127.6**
Incidence density[e]	**0.1**

[a]from Trials 25077IL/0048; total number of patient 184, glucose data available from 163 patients [b]% uses total number of patients in baseline sub-group as a denominator [c]Baseline glucose value is missing for one patient with glucose >200 mg/dL post-baseline
[d]Total patient year exposure is defined a the sum of days on treatment for each patient, divided by 365
[e]Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure
N is the number of patients with both baseline and end of treatment glucose data

The proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the short-term trials was low in all treatment groups (an incidence density of 0.4, 0.1 and 0 in the Seroquel, placebo and chlorpromazine groups, respectively). Similarly, the proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the long-term trials was low in both treatment groups (an incidence density of 0.1 and 0.2 in the Seroquel and haloperidol groups, respectively), and in the long-term trial in elderly subjects (incidence density 0.1).

The proportion of patients with a postbaseline glucose value ≥ 200 mg/dl did not increase as duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

Patient profiles

These data were based on random plasma glucose assessments and are therefore expected to fluctuate depending on the interval since the last meal, glucose content of the last meal, the state of hydration of the patient and many other factors. In order to make a thorough assessment on the effect of Seroquel treatment on plasma glucose levels, narratives of all patients with a glucose value ≥ 200 mg/dl at any time have been prepared and analysed to assess whether the elevated levels were consistent or sporadic, whether they were extreme, and whether any of the patients concerned had symptoms of diabetes. Full details are provided below.

In total, 20 patients had a plasma glucose level ≥ 200 mg/dl. Of these, three patients received haloperidol, one patient received placebo and 16 patients received Seroquel.

Three patients who received haloperidol (0012/1205,0021,2105, 0035/3502) had post baseline glucose values >200mg/dl. Two of them had baseline glucose values >200mg/dl and all three had histories of hyperglycemia or diabetes.

The single placebo patient with post baseline hyperglycemia had a baseline glucose of 142 mg/dl. Four of six post baseline assessments including the final assessment were in excess of 200mg/dl.

A review of the 16 patients who received Seroquel does not suggest a diabetogenic effect of Seroquel, as discussed below:

Patients with a baseline glucose value < 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Twelve of the 16 patients treated with Seroquel had a baseline glucose value < 200 mg/dl and at least one post-baseline glucose value ≥ 200 mg/dl.

In five of the 12 patients the last glucose value was >200mg/dl. In three of these five patients (0001/0021,0026/2607 and 0034/3411) the baseline value was elevated and slightly less than 200mg/dl (178mg/dl, 192mg/dl and 186mg/dl, respectively). In the remaining two patients,

repeated hyperglycemia was not observed since only the last glucose determination was >200mg/dl.

Seven of the 12 patients had baseline glucose values <200 mg/dl, a last glucose of <200 mg/dl and at least one post baseline assessment of >200 mg/dl. In six of these seven patients only one of several post-baseline assessments was >200 mg/dl. In the seventh of these patients three of six determinations were >200 mg/dl, but the last glucose value was 149.5 mg/dl, only 7.2 mg/dl greater than the baseline value.

Thus in these 12 patients, sustained hyperglycemia was not observed and the sporadic glucose elevations were not extreme. Further, *none* of the patients had classic symptoms of diabetes, such as polyuria, polydipsia and unexplained weight loss. The glucose values observed are plausibly understood as variations in a parameter that is strongly influenced by the interval since the last meal, glucose content of the last meal, state of hydration and many other factors.

Patients with a baseline glucose value ≥ 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Four of the 16 patients treated with Seroquel had a baseline glucose value ≥ 200 mg/dl and at least one post-baseline glucose value ≥ 200 mg/dl. Two of the four patients (0019/1903, 0023/2310) had a history of diabetes. A third had a history of hypothyroidism (0013/1309). The fourth patient's (0020/0005) final blood glucose was lower than baseline.

4.3 Discussion

4.3.1 Adverse event data

A total of 3506 patients were exposed to Seroquel across the Phase I, short- and long-term controlled Phase II/III, and uncontrolled trials in the Integrated safety database prepared for the original registration dossier.

The incidence of patients with adverse events possibly associated with disturbances in glucose regulation in patients treated with Seroquel was low across all the trial pools analyzed (1.6% in the Phase I trials, 1.6% in the short-term Phase II/III trials [≤ 6 weeks duration], 5.0% in the long-term controlled [> 6 weeks duration] and 4.0% in the uncontrolled trials) and, after adjusting for time-on-study, the incidence of adverse events possibly associated with disturbances in glucose metabolism did not increase as the duration of exposure to Seroquel increased (incidence density of 0.4 for the Phase I trials, 0.2 for the short-term Phase II/III trials, 0.2 for the long-term controlled trials, and 0.1 for the uncontrolled trials).

No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Diabetes mellitus was reported in five of 3506 patients (0.1%). All five cases were reported in the uncontrolled trials. Two of the five patients had a history of diabetes. A third patient is reported to have 'recovered' from the diabetes following treatment with glibenclamide and continued treatment with Seroquel. None of the five cases of diabetes mellitus were considered by the investigator to be related to trial therapy. Further, none of the cases were considered serious by the investigator or led to withdrawal of treatment.

The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (a total of 86 of 3506 patients, 2.5 %). (Note: this refers to patients with *any* weight gain, irrespective of the magnitude of the gain). Only one of the 3506 patients with weight gain in the clinical trial program had diabetes mellitus. This patient had diabetes at baseline (for which they were receiving treatment) and subsequently had 'poorly controlled' diabetes recorded as an adverse event.

There was one death due to adverse events possibly associated with disturbances in glucose dysregulation. The patient concerned is noted to have died of myocardial infarction. Hyperglycemia, as well as severe pancreatitis, dehydration, pneumonia, hyponatremia and hyperkalemia, were all noted in concurrence with the myocardial infarction. The patient in question was 77-year-old and had a history of borderline diabetes mellitus.

A total of four of 3506 patients (0.1%) were withdrawn from treatment due to events possibly associated with glucose dysregulation. Three patients were withdrawn due to hyperglycemia.

One of the three patients died; this patient is described above. Of the remaining two patients, one was a known diabetic with a history of hyperglycemia before entering the trial, and the other had a history of borderline elevated glucose levels. In all three cases, the investigator considered the hyperglycemia events to be serious, but unrelated to treatment with Seroquel. A further patient was withdrawn due to weight gain. Somnolence and abdominal distension were also documented as reasons for withdrawal in this patient. The weight gain was not considered serious by the investigator.

Apart from the three cases of hyperglycemia mentioned above, none of the other events possibly associated with disturbances in glucose regulation were considered serious by the investigator.

Obesity can be a risk factor for diabetes. The latest analyses (from Trial 5077IL/0051) have shown that Seroquel has a minimal effect on weight gain in the long-term, at all doses.

4.3.2 Plasma glucose data

The differences between the treatment groups in the mean change from baseline in plasma glucose data in short-term trials and long-term trials were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine [short-term trial] or Seroquel versus haloperidol[long-term trial]).

The proportion of patients with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

4.4 Conclusion

In conclusion, a thorough review of all the adverse event data and plasma glucose data in the clinical trial program has revealed no clear evidence of a causal association between Seroquel treatment and disturbances in glucose regulation. In addition the clinical trial data indicate that Seroquel has a minimal effect on weight gain in the long-term, at all doses.

5. REVIEW OF POSTMARKETING DATA

A search of the AstraZeneca safety database (Clintrace) for Seroquel spontaneous postmarketing reports of hyperglycemia or diabetes received from Japan since the approval of Seroquel in July 1997 through 02 October 2002 was performed. In addition, Clintrace was searched for all reports of hyperglycemia or diabetes for Seroquel received for the same period from all other countries. A total of 93 glucose related reports have been received by AstraZeneca to date. Of these, 13 were received from Japan. The reports from Japan will be discussed separately, followed by all other glucose adverse events reports. Narratives for all the reports from Japan and any other reports of interest are contained in the appropriate sections that follow.

5.1 Reports from Japan

From 31 July 1997 (international birthdate for Seroquel) through 02 October 2002, 13 reports have been received from Japan including; new onset diabetes mellitus (1), hyperglycemia in patients with no prior history of diabetes (2), exacerbation of diabetes (5), and diabetic ketoacidosis (DKA) or possible DKA (5). These reports along with narratives, comments, and analysis are presented below.

5.1.1 New Onset Diabetes

There was one report of newly diagnosed diabetes mellitus.

2002AP00269 (200200382): This serious report of "Diabetes mellitus NOS" described a 29-year-old female patient who was receiving Seroquel for neurosis. Seroquel (50 mg/day) was titrated up to 500 mg/day by the 19th day. About two weeks later, an examination revealed a fasting blood sugar (FBS) of 394 mg/dl and HbA1c of 8.6%. The patient weighed 92 kg and her height was 161 cm. Diabetes mellitus was diagnosed. Seroquel was decreased to 400 mg/day. Five and one-half weeks after the first dose of Seroquel, the patient was hospitalized for the treatment of diabetes mellitus. The following day thirst and nausea developed. The FBS was 457 mg/dl and HbA1c was 14.8%. The next day insulin therapy was started. Two days later Seroquel was discontinued and six days later the FBS had decreased to 129 mg/dl, so insulin therapy was discontinued that day. Two weeks later the FBS had increased slightly to 145 mg/dl and her weight was 92.2 kg. Metformin and nateglinide were started. Three and one half months after being hospitalized the FBS was 99 mg/dl, weight was 97.8 kg and the patient was discharged from the hospital. Two weeks later the FBS was 99 mg/dl and HbA1c was 4.4%. The event was considered improved. Medical history included obesity, and excessive eating. Concomitant medications included Celtect (oxatomide), Blopress

(candesartan), Alesion (epinastine), Rohypnol (flunitrazepam), and Hirnamin (levomepromazine).

Comment: The elevated HbA1c indicates that hyperglycemia was present for the past two to three months, but the patient was on Seroquel for only the previous past month. Thus, the hyperglycemia preceded Seroquel treatment. In addition, the patient had a history of excessive eating and was obese prior to starting Seroquel. Obesity is a risk factor for type II diabetes mellitus.

5.1.2 Hyperglycemia in patients with no prior history of diabetes

There were two reports of hyperglycemia in patients with no prior history of diabetes.

2002AP02947 (200205325): This report of "Hyperglycaemia NOS" involves a 44-year-old female patient who has been receiving Seroquel (100 mg/day) for the treatment of schizophrenic psychoses. The patient was concomitantly receiving carbamazepine, tiapride, sofalcone, biperiden, and magnesium oxide. The patient did not have a family history of obesity or diabetes mellitus. After 33 weeks and five days of Seroquel therapy, on 02 September 2002, the patient developed a fever (temperature 38 ^{0}C). Three days later, with a body temperature of 38.3 ^{0}C, a physician saw the patient, diagnosed an aggravation of the patient's mental state, treated her with diazepam 10 mg IM, haloperidol 1 amp IM, and fluphenazine 250 mg IM. On 08 September 2002, the patient visited the physician as she had not taken food or drink for six days. An infusion solution was administered to provide nutrition and hydration. Haloperidol 1 amp was mixed to the solution. By the next day, she had not consumed food for several days, weighed little more than 40 kg, was reported to have had an immeasurable blood pressure, a blood sugar level of 300 mg/dL, and was hospitalized. On 10 September 2002, her condition was reported to have improved, however, laboratory tests revealed a creatinine of 5.1 mg/dL and a blood urea nitrogen (BUN) of 114 mg/dL. During the early hours of the 11 September 2002, her blood pressure and consciousness decreased again and she did not respond when called. Oxygen measured at fingertip was decreased to less than 80%, her body temperature was 37.4 °C, WBC 13,300/mm^3, and she had no rigidity. The patient was considered to be suffering from dehydration, a decrease of urinary volume, disturbed consciousness, and the possibility of cerebral vascular disturbance and neuroleptic malignant syndrome (NMS) were considered. She was transferred to another hospital. On arrival she was in a deep coma with an immeasurable blood pressure. A blood examination revealed hyperglycemia (blood sugar noted to be 1057 mg/dL), acidosis, and hypernatremia. CPK was 2,124 u/L. She was treated with intravenous fluids. The next day hemodialysis with continuous hemofiltration was started. The CPK was 15,215 u/L and blood sugar was 535 mg/dL. Disseminated intravascular coagulation (DIC) was noted. The following day, hyperglycemia, acidosis, hypernatremia, and dehydration resolved. The CPK peaked on 14 September 2002 at 78,690 u/L and dantrolene was started. On 16 September 2002 the DIC resolved. On 17 September 2002 the temperature was 38.7 °C and WBC 14,400/mm^3. On 19 September 2002 the CPK decreased to 2225 u/L and NMS was considered resolved. Continuous hemofiltration was stopped and the patient was transferred out of intensive care unit (ICU) the following day. A HbA1c (date not reported) was reported

to be 6.4%. A physician from the first hospital reviewed the patient's blood sugar levels and considered the hyperglycemia to be chronic, but not severe.

Comment: The labeled event, hyperglycemia (not diabetes) was likely to be pre-existing. Based on the HbA1c and the physician at the first hospital, it appears the patient had some chronicity to her hyperglycemia. The HbA1c of 6.4% is slightly elevated. She may have had an infection (fever and increased WBC) that precipitated an acute increase in blood glucose. Infections are common precipitators of non-ketotic hyperosmolar coma or diabetic ketoacidosis in diabetes. IV haloperidol is a plausible explanation for the NMS. Other confounding factors include the dehydration, which may have caused or contributed to the increased CPK by rhabdomyolysis, as well as the possibility of infection as an explanation for the fever. Furthermore, the concomitant medications carbamazepine and tiapride have also been reported to cause NMS.

2001AP02034 (200101809): This report of "Blood glucose increased" involves a 57-year-old woman who has been receiving Seroquel 600 mg for the treatment of schizophrenia. The patient was also receiving haloperidol, trihexyphenidyl, alprazolam, levomepromazine, nitrazepam, sennoside, and pantethine as concomitant medication. On 14 March 2001 the patient commenced treatment with quetiapine 75 mg/day which was increased to 150 mg/day on 21 March 2001, 300 mg/day on 28 March 2001, and 600 mg/day on 6 April 2001. On 17 April 2001 she developed a fever of 38.1 ^{0}C, which was decreased by hydration and cooling to 37.0-37.9 ^{0}C. The following day her temperature was 37-38.1 ^{0}C, WBC=6880, CRP=3.53, and CPK=521. Tube feeding commenced. On 19 April 2001 slight muscle rigidity of the extremities was noted. All medications were discontinued on 21 April 2001. Her temperature increased to 40 ^{0}C, BP varied from 100/54 to 160/112, and at one time was unmeasurable, and her CPK increased to 1053. Her symptoms were considered to be NMS. She was transferred to another hospital on 23 April 2001. During that hospitalization she was treated for pneumonia and a generalized convulsion. The patient received Dantrium (dantrolene), Shiomarin (latamoxef), Horizon (diazepam), and Aleviatin (phenytoin). On 30 April 2001 the patient was transferred to a psychiatric/neurological ward, with normal vital signs, rigidity and drowsiness. On 02 May 2001 Parlodel (bromocriptine; 7.5 mg/day) was started. On 06 May 2001 Ensure (parenteral nutrition) was started with transnasal administration. On 07 May 2001 dantrolene (75 mg/day) and bromocriptine (15 mg/day) were started. The patient's blood sugar level increased to 413 mg/dL, but this returned to a normal level after the patient received calorie controlled treatment. Later she had hallucinations and delusions, and Melleril (thioridazine; 50 mg/day) and Artane (trihexyphenidyl; 5 mg/day) were added and the dosages titrated upwards. On 25 June 2001 the patient was transferred back to the previous hospital with the following prescribed drugs: Parlodel, Dantrium, Melleril, Artane, Gasmotin (mosapride), Toughmac-E (digestive enzyme preparation), Wintermin (chlorpromazine; labeled for hyperglycemia), Benzalin (nitrazepam), and Pursennid (sennoside).

Comment: This report of an isolated elevated blood glucose is confounded by a complicated medical course and multiple medications.

Summary of reports of hyperglycemia: Of these two reports of hyperglycemia in patients without a prior history of diabetes, one (2002AP02947 (200205325)) has some chronicity to her hyperglycemia, with an acute increase in blood glucose, possibly precipitated by an infection. The other (2001AP02034 (200101809)) described an isolated elevated blood glucose, confounded by a very complicated medical course and multiple concomitant medications.

5.1.3 Exacerbation of Diabetes

There are five reports of exacerbation of diabetes.

2002AP02570 (200204425): This serious report of "Diabetes mellitus aggravated" concerns a 26-year-old female patient who was receiving Seroquel for schizophrenic psychoses. The patient had a history of non-insulin dependent diabetes mellitus, bulimia nervosa, and obesity (height 155 cm and weight 91 kg). The patient's concomitant medications included flunitrazepam, quazepam, bromocriptine, sodium valproate, levomepromazine, and zotepine. On 10 May 2001, the patient's therapy was switched from sodium valproate and zotepine to Seroquel and zotepine due to a fasting blood sugar level of 170 mg/dL (analysed five hours after lunch) and an HbA1c level of 6.6 %. In July 2002, blood examination revealed hyperglycaemia, with a blood sugar level of 300 mg/dL and HbA1c of 10 %. The patient drank large volumes of juice and disclosed that this habit continued after commencement of Seroquel therapy. On 9 August 2002, she was admitted to the hospital and her body weight was 85 kg. Treatment included a diet of 1200 kcal/day and Basen (voglibose; 3 tab/day). On 14 September 2002, when the patient was discharged from the hospital, her body weight was 79 kg, and blood sugar level improved to 103 mg/dL. On 26 September 2002, the patient visited the reporting physician. Diet of 1200 kcal and treatment with voglibose was continued at home. Body weight was 78 kg.

Comment: This report of exacerbation of diabetes is confounded by the patient's diet (large volumes of juice). While continuing Seroquel, the patient became better controlled with diet, weight reduction, and initiation of an oral hypoglycemic drug.

2002AP03075 (200205593): This report of "Hyperglycaemia NOS" and possible "Diabetic ketoacidosis" involves a 66 year-old male patient who was receiving Seroquel for the treatment of schizophrenic psychoses. The patient was concurrently suffering from diabetes mellitus and was also receiving biperiden, acarbose, glibenclamide, Tsumura-100, sodium picosulfate, brotizolam, flunitrazepam, carbamezepine, atorvastatin, and magnesium oxide. Before Seroquel treatment commenced the patient had a fasting blood sugar of 179. Treatment with Seroquel (125 mg/day) was commenced on 27 April 2001 and by 17 May 2001 the patient had a fasting blood sugar level of 300. An oral anti-diabetic drug was administered but the patient still had a fasting blood sugar level of 250. On 5 July 2001 (the patient was receiving a dose of Seroquel 200 mg/day at this time), Seroquel treatment was withdrawn. The fasting glucose levels remained elevated.

Comment: This report of exacerbation of diabetes described a negative dechallenge.

2002AP03102 (200205220): This report of "Hyperglycaemia NOS" involved a 65-year-old female patient who was receiving Seroquel (200 mg/day) for schizophrenia. She has had a history of diabetes mellitus since 1984. The patient's blood sugar level was controlled with oral antidiabetic drugs. She was concomitantly receiving risperidone (reported to be associated with diabetes), periciazine, trihexyphenidyl, itraconazole, galenicals, glibenclamide, dimeticone, and acarbose. On 11 April 2002, thirty-nine weeks after commencing treatment with Seroquel, the patient experienced the event of hyperglycemia, with no subjective symptoms. On 2 August 2002, regular examination revealed a marked increase of blood sugar level two hours after a meal (no values provided). On 05 September 2002 regular examination revealed further increase of blood sugar levels both fasting and two hours after a meal. Treatment with Seroquel was stopped on 10 September 2002. The event was considered to be life threatening. At the time of reporting to AstraZeneca (three weeks after Seroquel was discontinued), the patient had not recovered from the event. A detailed examination is being conducted to detect some internal organ disease such as pancreatic tumor, which may have caused the event.

Comment: This report described a negative dechallenge based on the lack of recovery three weeks after discontinuation of Seroquel. In addition, this report is confounded by a concomitant medication associated with diabetes.

2001AP04051 (200103951): This serious report of "Hyperglycaemia NOS" described a 44-year-old male patient who was receiving Seroquel (50 mg/day) for the treatment of schizophrenic psychoses. Before treatment with Seroquel the patient's diabetes mellitus was well controlled (treatment not specified) with an HbA1c of 6.5%. Four weeks and three days after the first dose of Seroquel the patient experienced an event of hyperglycaemia. The HbA1c increased to 9.2% and the blood sugar increased to 486 mg/dl. One month after the onset of events the patient's HbA1c increased to 12.1% and the blood sugar was still increased at 254 mg/dl. The patient admitted drinking a large amount of fruit juice. The patient was hospitalized three days later and dietary controls were introduced but lab values were still increased (HbA1c of 12% and blood sugar of 226 mg/dl). The patient was started on Euglucon (glibenclamide) without improvement. Seroquel was discontinued six weeks and three days after the event. The blood sugar started to decrease and glibenclamide was discontinued one month later. Seventeen weeks and three days after the onset of events the patient recovered. Medical history included hyperlipidemia, diabetes mellitus, and mania with risperidone use. Concomitant medications included Amoxan (amoxapine; labeled for hyperglycaemia), sulpiride, Cerekinon (trimebutine), Seniran (bromazepam), Akineton (biperiden), Ledolper (brotizolam), Atarax (hydroxyzine), Rohypnol (flunitrazepam), Myslee (zolpidem), Cremin (mosapramine), Bezatate (bezafibrate), and Telesmin (carbamazepine).

Comment: This report of an exacerbation of diabetes coincident with Seroquel therapy is confounded by the concomitant medication amoxapine, which has been reported to be associated with hyperglycemia. In addition, the patient admitted to drinking large volumes of fruit juice, which raises the possibility that dietary non compliance could be a chronic problem contributing to the hyperglycemia.

2002AP01913 (200203006): This report of "Blood glucose increased" involves a 59-year-old man who received treatment with Seroquel (200 - 400 mg/day) for schizophrenia. The patient had a history of non-insulin dependent diabetes mellitus (NIDDM), chronic hepatitis C, and hypertension. He was receiving sulpride, biperiden, chlorpromazine/promethazine/phenobarbital combination (labeled for hyperglycemia/diabetes), brotizolam, nitrazepam, flunitrazepam, benidipine, enalapril, candesartan cilexetil, terazosin, lansoprazole, and tamsulosin concurrently. On 26 April 2001, the patient was admitted to hospital. He was unable to follow, and resisted, dietary therapy for diabetes mellitus, and was prescribed a 2000 kcal diet. During July and August 2001, his mental status became worse, and he complained of auditory hallucinations, insomnia and feeling irritated. The patient was referred to an isolation room, and all oral drug therapies withdrawn. The patient received treatment with haloperidol, biperiden, and diazepam. He was prevented from eating between meals and his weight decreased from 72 kg to 65 kg. His blood sugar level was satisfactory. He was then returned to the general ward. Seroquel was begun on September 2001 and he continued on a dose of 200 mg/day. His bodyweight gradually increased again due to consumption of soft drinks, and eating after scheduled meals. Levels of HbA1c were in the normal range. In April 2002, after Seroquel had been increased to 400 mg/day, HbA1c increased from 5.9% to 8.6%. His maximum blood sugar level was noted to be 410 mg/dL. The patient agreed to stop eating between meals. On 08 May 2002, treatment with pioglitazone was initiated, and the blood sugar level decreased. Seroquel therapy continued at a dose of 400 mg/day.

Comment: This report of exacerbation of diabetes is confounded by a history of non-compliance with diet. Seroquel therapy was continued.

Summary of reports of exacerbation of diabetes: Of these five reports of exacerbation of diabetes, four are confounded by diet or concomitant medications or both (2002AP02570 (200204425); diet, 2002AP01913 (200203006); diet, 2001AP04051 (200103951); diet and amoxapine (hyperglycemia), and 2002AP03102 (200205220); risperidone. This last case also described a negative dechallenge, i.e. the exacerbation of diabetes continued even after Seroquel was discontinued. The remaining report (2002AP03075 (200205593) also described a negative dechallenge.

5.1.4 Diabetic Ketoacidosis

There are four reports of diabetic ketoacidosis and one report of possible diabetic ketoacidosis. The narratives are provided below.

2002AP01163 (200202573): This serious report of "Diabetic ketoacidosis" and "Diabetic coma NOS" described a 36-year-old male patient who had a medical history of type II diabetes mellitus and drinking excessive amounts of soft drinks and coffee. The patient had been drinking large volumes of soft drink and his blood glucose level and HbA1c were 776 and 10.7 %, respectively. Treatment included a drip infusion with added insulin and eventually oral pioglitazone. After six months of pioglitazone therapy, the blood glucose level was 109 (2 hr value) and HbA1c was 5.3%. On 18 July 2001, his blood glucose was increased to 331 (4 hr value) due to drinking excessive amounts of coffee and HbA1c was 13.9. On 28

January 2002, the patient reported that he stopped taking pioglitazone but his blood glucose was 117 (4 hr value); HbA1c was 4.9 and body weight was 59 kg. On 15 April 2002, blood glucose was 420 (2 hr value) and HbA1c was 8.2. The patient was being treated with Clofekton (clocapramide) and on 15 May 2001, Seroquel (25 mg/day) was added. The dosage of Seroquel was increased and decreased over the next few months until it was discontinued on 07 September 2001 when it was switched to clocapramide. On 18 April 2002, clocapramide (75mg/day) was switched to Seroquel (75 mg/day). Two days later the patient's mental status was unchanged and he had no physical complaints. On 25 April 2002, his mental status was unchanged, though he felt terribly unwell. On 30 April 2002, the patient was admitted to the hospital in a deep coma. Blood pressure was 60/36 mmHg, pulse was 120 bpm, and blood glucose was 1570. Renal failure developed secondary to severe dehydration, and right heart collapse or shock. Treatment included continuous large volume infusion with drip infusion of insulin and noradrenaline; which resulted in systolic BP of 90-100 mmHg. Immediately after, fever (~ 40 ^{O}C) was recorded. Antibiotic therapy with ampicillin, sulbactam, and clindamycin was started. FOY (gabexate mesylate) was started for disseminated intravascular coagulation (DIC) and L-Aspartate potassium was given for hypokalemia. "The condition was almost hyperglycemic hyperosmolar nonketotic coma (HHNC)." On hospital day two, his respirations were weak. Blood gas analysis revealed carbon dioxide narcosis. Urinary ketone body (-), pH 5, microbial tests showed urinary test was negative, however, sputum test result was suspected BLNAR (beta-lactamase negative ampicillin resistant), haemophilus influenza (1+), streptococcus a-haemolyticus (1+), and candida albicans (1+). The patient was intubated, and put on a respirator. The fever continued. Antibiotics were changed to imipenem and cilastatin. Abdominal computed tomography (CT) and echography were carried out to detect the cause of the fever, but infection could not be detected. Blood analysis also excluded the possibility of infection. CNS disorder was suspected due to anisocoria and weak/absent spontaneous respiration. Brain stem lesion was suspected, since brain edema, hemorrhage, and major infarction were not recognized on brain CT. Concerning the fever, hyper-myoglobinemia was recognized on blood gas analysis data, and it was considered necessary to rule out NMS since he was taking Seroquel, though muscle findings were few. Dantrolene was given with injection for diagnostic treatment. Acute renal failure occurred due to the hyper-myoglobinemia, but dialysis could not be started, since BP was decreased (around 60-70 mmHg) and gastro-intestinal (GI) bleeding occurred due to DIC. Catecholamine resistant hypotension (shock) occurred and the patient subsequently died. The cause of death was diabetic ketoacidosis. The physician commented that the patient had not been compliant with his diet. NMS was suspected to have caused the hyper-myoglobinemia but there were few clinical and physical findings. Rhabdomyolysis may have occurred after peripheral circulatory failure, dehydration severe enough to cause shock in the condition of ketoacidosis, and central fever. No further information was provided.

Comment: A detailed review of the laboratory data indicated that the HbA1c was markedly elevated at 11.8 on 30 April 2002, twelve days after starting Seroquel. Since the HbA1c indicates glucose control for the previous two to three months, this elevated level suggests poor diabetic control for a couple months before Seroquel was initiated. The patient's history of non-compliance with diet (excessive consumption of soft drinks) and medication (stopped

oral hypoglycemic pioglitazone) would account for poor diabetic control. In addition, infection, which was suspected in this case, is a common precipitator of diabetic ketoacidosis. Thus, this case is confounded.

2002AP01772 (200203342): This serious report of "Diabetic ketoacidosis" described a 51-year-old male patient who received Seroquel and Risperdal (risperidone; labeled for diabetic ketoacidosis and hyponatremia) for schizophrenic psychosis, and developed diabetic ketoacidosis. The patient was hospitalized for four months. Urinary glucose levels were analyzed monthly and remained negative during this time. Risperdal (2 mg/day) was initiated upon hospitalization and increased to 4 mg/day by two months. About six weeks later, Seroquel (200 mg/day) was initiated and titrated to 300 mg/day within eight days. About six weeks after discharge blood tests revealed mild anemia, slightly increased triglycerides, and normal glucose (not fasting) and HbA1c values (123 mg/dl and 4.8 %, respectively). About six months later, the patient's condition seemed uneventful except for a complaint of insomnia, for which his nitrazepam dose was increased (as outpatient). Fifteen days later (42 and 48 weeks after beginning Seroquel and risperidone, respectively) the patient experienced "disturbed consciousness" and was hospitalized. Laboratory results included blood sugar level (1179 mg/dl), HCO3 (3.0 mmol/L), sodium (116.3 mmol/L), and potassium (6.55 mmol/L). Results of the blood gas analysis were; BE (base excess) -25.2, and pH 7.055. Diabetic ketoacidosis was diagnosed. Hydration status prior to hospitalization was unknown. All medications were discontinued and the patient was given normal saline, Myelon (sodium bicarbonate), and Novolin-R (insulin). The following day, blood glucose improved (233 mg/dl) but the patient remained comatose. Potassium levels had decreased (2.73 mmol/L) before increasing again (3.98 mmol/L) by the evening. During the evening, the patient's blood sugar increased to 545 mg/dl. Shock occurred and was unsuccessfully treated with a large volume of dopamine. The following day the patient died of circulatory failure (not confirmed that the patient died from a hyperosmolar coma). An autopsy was not performed. The patient's sister confirmed that the patient drank about 4 liters of Coca-Cola every day for the last five weeks, and that the patient had lost weight rapidly in the last few weeks. Medical history included hepatic failure and acute hepatitis, which were suspected to be drug induced (drug not identified), prior to the diabetic ketoacidosis. Concomitant medications included Meilax (ethyl loflazepate; 4 mg/day) and Benzalin (nitrazepam; 20 mg/day). Family history for diabetes mellitus was unknown.

Comment: Blood glucose and HbA1c levels months after starting Risperdal and Seroquel were normal. The diabetic ketoacidosis occurred after almost a year of therapy with Risperdal and Seroquel and several weeks after drinking four liters of Coca-Cola daily. Thus, this report is confounded both by diet (drinking large amounts of Coca-Cola) and a concomitant medication (Risperdal).

2002AP02304 (200203907): This serious report of "Diabetic ketoacidosis" described a 31-year-old male patient who was receiving Seroquel for treatment of schizophrenia. Three months after Seroquel was increased to 600 mg/day, the patient complained of limb weakness and a limp, which were not recognized objectively. Two days later the dysarthria and limb weakness worsened. The next day, approximately one and one-half years after commencing

Seroquel, the patient was hospitalized (he could not hold a cup in his hand). On admission, the patient was almost "conscious", deep reflex was mildly increased, BP was 138/86, pulse 100 bpm, blood sugar 1348 mg/dl, and temperature was 37.9°C. Two days later, brain CT was normal, and blood sugar level was 1280 mg/dl and urinary sugar 4+. Treatment included insulin and infusion solution. The event resolved the following day. It was unknown if the patient was discharged on insulin. The reporting physician considered that the event was related to "PET bottle syndrome" (drinking large amounts of sweetened soft drink; other details are unknown). Medical history included obesity. Concomitant medications included haloperidol, biperiden, trihexyphenidyl, chlorpromazine, levomepromazine, and chlorpromazine/promethazine/phenobarbital.

Comment: The reporting physician considered the event related to drinking large amounts of sweetened soft drink.

2002AP02329 (200203901): This serious report of "Diabetic ketoacidosis" described a 21-year-old female who was receiving Seroquel (600 mg/day) for the treatment of schizophrenia. The patient stopped oral medications and insulin and as her psychiatric symptoms were aggravated and vomiting occurred. Three days later (about eight weeks after starting Seroquel) the patient was hospitalized with vomiting, "deterioration of consciousness", blood sugar level of 745 mg/dl, WBC of 29,2000/mm3, C-reactive protein (CRP) of 1.28 mg/dl, and moderate dehydration. DKA was diagnosed. Treatment included drip infusion of normal saline, electrolytes with glucose drip infusion, and insulin infusion. Blood sugar, blood gases and mental status all improved. The next day the blood sugar was 276 mg/dl. The following day oral drugs (risperidone, biperiden, carbamazepine, flunitrazepam, and levomepromazine) were started. The day after that, auditory hallucinations and delusion "continued". Blood sugar was stable with a mean blood sugar of 200-300 mg/dl; urine ketones and sugar were both negative. Two days later the blood sugar again improved with a mean of 100-200 mg/dl. Auditory hallucinations and delusions still continued but insomnia did not occur. On the seventh day of admission the event had improved. Medical history included insulin dependent diabetes mellitus (IDDM) since age five. Concomitant medication included trihexyphenidyl, carbamazepine, haloperidol, clonazepam, flunitrazepam, zotepine, levomepromazine, and human insulin.

Comment: This patient had a history of insulin dependent diabetes mellitus since the age of five, and had a history of non-compliance (stopped her insulin). The high WBC may also have indicated an infection. Infections can precipitate diabetic ketoacidosis.

2002AP02883 (200205214) This report of possible diabetic ketoacidosis involved a 30-year-old female patient who has been receiving Seroquel for the treatment of schizophrenic psychoses. The patient was concomitantly receiving haloperidol (30 mg/day gradually reduced to 5 mg/day), bromperidol (12 mg/day), biperiden (3 mg/day), triazolam (0.5 mg/day), flunitrazepam (1 mg/day), and distigmine bromide. The patient did not have a history of drinking or alcoholism, it is unknown whether her family had a history of diabetes mellitus, but the patient did not. Seroquel treatment (75 mg/day) was commenced in June 2001. This was titrated upwards to 200 mg while haloperidol was reduced from 30 mg to 5 mg. On 7

September 2002, one year and three months after commencing Seroquel treatment the patient developed symptoms of what was reported to be a common cold (diarrhea, retching, vomiting and pyrexia) and her body temperature increased to 38-39 °C. On 8 September 2002, her fever resolved but gastrointestinal symptoms continued and anorexia occurred. On 9 September 2002 her diarrhea and vomiting continued and she received treatment with a drip infusion to prevent dehydration. During the evening her family recognized she was drinking a large amount of water, later that night the patient complained of difficulty breathing. On 10 September 2002, her difficultly breathing continued and she visited a local internist. Chest and abdominal X-ray results were normal; laboratory tests were not performed. The internist diagnosed the condition as psychiatric symptoms. She returned home after treatment with a drip infusion. During the evening her difficulty breathing increased. Her family recognized a sudden change in her condition and called an ambulance. At this time the patient possibly experienced a cardiac arrest. She underwent intubation, no vomit was recognized at the time and she died at approximately 1900 hours. Her body weight had not markedly changed recently and she had a normal physique, due to this her blood sugar level had not been analyzed recently. Her eating habits were normal for a person of her age. The patient continued to receive Seroquel until the day of her death. An autopsy has been performed, but the cause of death could not be determined. A detailed examination is being carried out histologically. The reporting physician considered that the diarrhea, pyrexia, retching, and vomiting were related to a common cold and commented that the patient was healthy, but it was assumed that the hyperglycemia, which may have occurred after diabetes mellitus, was triggered by the common cold. The physician considered that Seroquel caused the condition, since another patient developed hyperglycemia during Seroquel therapy. However, it is only a matter of speculation, since there was no objective data. Since excessive drinking and breathing difficulty occurred, the reporter also suspected that ketoacidosis possibly occurred and advanced to induce deterioration of her condition and death. It was considered that cardiac arrest possibly occurred due to hyperkalemia in such a condition.

Comment: The possibility that this case represented diabetic ketoacidosis was acknowledged by the reporting physician to be speculative because no laboratory blood tests (e.g. glucose, pH etc) were drawn. This patient had symptoms that were diagnosed as a common cold, but may have been gastroenteritis. In addition, the symptoms of nausea, vomiting, and diarrhea are also adverse events associated with distigmine, one of her concomitant medications. In summary, there was no objective data to support a diagnosis of diabetes or diabetic ketoacidosis, and possible alternative explanations for the events exist.

Summary of reports of diabetic ketoacidosis: All four reports of diabetic ketoacidosis are confounded. In two reports (2002AP01772 (200203342), 2002AP02304 (200203907)), the patients had no prior history of diabetes, but drank large amounts of sugar-containing beverages. In one report (2002AP02304 (220203907)), the reporting physician specifically attributed the event to drinking large amounts of sugar-containing beverage. In the other report (2002AP01772 (200203342)), the patient was also receiving Risperdal. In the remaining two reports of diabetic ketoacidosis, the patient had a history of diabetes prior to starting Seroquel (2002AP01163 (200202573), 2002AP02329 (200203901)). In one of these (2002AP01163 (200202573)), the HbA1c level indicated the patient's diabetes was poorly

controlled prior to receiving Seroquel. This patient also had a history of non-compliance with both diet and medication. In the other (2002AP02329 (200203901)), the patient also had a history of non-compliance with her diabetes medication. In both these reports, there was infection or possible infection. Infections can precipitate diabetic ketoacidosis. There was an additional case (2002AP02883 (200205214)) of possible diabetic ketoacidosis, but there was no laboratory data to support a diagnosis of diabetes or diabetic ketoacidosis, and there was a viral illness that could account for many of the symptoms or could have precipitated a diabetic ketoacidosis, if it did occur.

5.1.5 Summary of the reports from Japan

In the one report of new onset diabetes (2002AP00269 (200200382)), the HbA1c level indicated hyperglycaemia prior to Seroquel. Of the two reports of hyperglycemia in patients without a known history of diabetes, one (2002AP02947 (2002205325)) was consistent with infection precipitating an acute increase in blood glucose and the other (2001AP02034 (200101809)) represents an isolated elevated glucose level in a long, complicated medical course involving multiple medications.

Of these five reports of exacerbation of diabetes, four are confounded by diet or concomitant medications or both (2002AP02570 (200204425); diet, 2002AP01913 (200203006); diet, 2001AP04051 (200103951); diet and amoxapine (hyperglycemia), and 2002AP03102 (200205220); risperidone. This last case also described a negative dechallenge, i.e. the exacerbation of diabetes continued even after Seroquel was discontinued. The remaining report (2002AP03075 (200205593) also described a negative dechallenge.

Of the four reports of diabetic ketoacidosis, two (2002AP02304 (200203907), 2002AP01772 (200203342)) occurred in patients without a known history of diabetes, but who had been drinking large amounts of sugar-containing beverages; and two (2002AP01163 (200202573), 2002AP02329 (200203901) occurred in patients with a known history of diabetes, with a history of non-compliance with diet or medication or both, and had infection or possible infection precipitating the event. In one of these two (2002AP01163 (200202573)), a HbA1c level documented poor diabetes control prior to Seroquel. There was one report (2002AP02883 (200205214)) of possible diabetic ketoacidosis, but no objective data (e.g. glucose or pH level) were collected to support this. This report is consistent with a viral infection and many of the symptoms are expected adverse events with a concomitant medication.

5.1.6 Conclusion regarding reports from Japan

In summary, all these reports are confounded, had alternative explanations, had a negative dechallenge, or had documentation of hyperglycaemia or poor diabetes control prior to receiving Seroquel. These reports provide insufficient information to establish a causal relationship between Seroquel and diabetes, hyperglycaemia, exacerbation of diabetes, or diabetic ketoacidosis.

5.2 Reports from countries other than Japan

5.2.1 Diabetic ketoacidosis

Twenty-one reports containing the MedDRA preferred term "Diabetic ketoacidosis" were identified. Five of these reports (2002AP03075, 2002AP02329, 2002AP02304, 2002AP01772, 2002AP01163) were received from Japan and are discussed above in Section 6.1. The remaining 16 reports are discussed below. Four of these (2002UW08229, 2001UW12078, 2001UW05726, 1998UW49554) had an outcome of death.

5.2.1.1 Reports of diabetic ketoacidosis with no history of diabetes reported

2001UW12078: This serious report of "Diabetic Ketoacidosis" described a 57-year-old patient (sex unknown) who was taking Seroquel (dose/duration unknown) for an unknown indication. The patient experienced diabetic ketoacidosis and died. Medical history was not provided. Concomitant medications included Risperdal (risperidone; labeled for diabetic ketoacidosis), which was also considered a suspect medication. No further information was obtainable.

Comment: Risperdal is labeled for diabetic ketoacidosis. Assessment of causality is difficult due to minimal information.

2002UW08229: This serious report of "Diabetic ketoacidosis" described a 40-year-old female patient who was receiving Seroquel for the treatment of schizoaffective disorder and a depressed mood. The patient's Seroquel dose was gradually titrated to 300 mg/day over several months. Five months later the dose was increased to 200 mg 2x/day. The patient misunderstood the directions and took 200 mg/day from that time on. Approximately four months later the patient was found dead on the floor of her apartment. The police investigator's report stated that the patient's neighbor disclosed that the patient traded drugs, namely cocaine, crack, and marijuana, to let others drive her car, and that the patient was very depressed and hated herself, and spoke of wanting to commit suicide. Marijuana residue and seeds were found in her car. The autopsy report indicated that the cause of death was DKA, with a contributing factor of diabetic renal failure. The report also revealed that the patient had severe fatty liver metamorphosis, cholelithiasis, congestion of the viscera, and obesity. Lab values at autopsy from a vitreous specimen included Na 146 mmol/L, K 25.5 mmol/L, chloride 107 mmol/L, BUN 86.5 mg/dl, glucose 997 mg/dl, and creatinine 2.7 mg/dl. The patient's urine was positive for cocaine metabolites, and her heart blood was positive for cocaine, ethanol, acetone, and sertraline. Medical history included mental illness, smoker, obesity (weight 186 lb./height 66 inches), and cocaine, crack, and marijuana abuse. Concomitant medications included Buspar (buspirone), Zoloft (sertraline; labeled for hyperglycemia), and Tequin (gatifloxacin).

Comment: The patient died from diabetic ketoacidosis with a contributing factor of diabetic renal failure. Diabetic renal failure suggests some degree of chronicity of diabetes that likely preceded Seroquel therapy. The patient had a history of cocaine, crack, and marijuana abuse and was taking sertraline, which is known to cause hyperglycemia.

2002UW09406: This serious report of "Diabetic ketoacidosis" described a 36-year-old male patient who was prescribed Seroquel (400 mg/day) for the treatment of schizophrenia. The day after starting Seroquel the patient was hospitalized for DKA. Treatment included 10 units of insulin IV and then 10 units/hour IV. Seroquel was discontinued and it was not reported if Seroquel was restarted. Lab values on admission included: blood gas pH 7.26, glucose 1544 mg/dl, K^+ 6.1, BUN 64, creatinine 3.5, and urine positive for ketones. (Units listed whenever they were provided). The patient did recover from the event and was discharged from the hospital. Medical history included gastroesophageal reflux disease and no family history of diabetes. Concomitant medications included Prevacid (lansoprazole; labeled for diabetes), ibuprofen, multivitamins, and Metamucil. No further information was provided.

Comment: The severity of the hyperglycemia (glucose level of 1544 mg/dl) suggests a time course longer than the one day the patient took Seroquel (single tablet). Thus, the time course suggests a cause other than Seroquel.

2002GB01741: This serious report of "Diabetic ketoacidosis" described a 50-year-old male patient who had been receiving Seroquel (800 mg/day for a least three years) for the treatment of schizophrenia. During Seroquel therapy the patient developed ketoacidosis and was admitted to the hospital. Seroquel was discontinued. Medical history included psoriasis and a reported body mass index of "70". It also was reported that the patient had no family history of diabetes. Concomitant medications included Adalat (nifedipine; labeled for hyperglycemia), Neotigason (acitretin), trazodone, and atorvastatin. At the time of the report the outcome was unknown.

Comment: Obesity was not reported but the patient had a reported BMI of "70". Obesity is a risk factor for type II diabetes. In addition, this report is confounded because the patient was taking a concomitant medication labeled for hyperglycemia.

2002GB01254: This serious report of "Diabetic ketoacidosis" described a male patient (age unknown) who was receiving Seroquel (300 mg/day) for the treatment of schizophrenia. One year and two months after starting Seroquel the patient was hospitalized with DKA. On admission, the glucose level was 46.6 (no units provided); the patient was dehydrated, and acidotic. The patient's HbA1c was >12%. Type I or type II diabetes was suspected. The patient had become increasingly obese (BMI 48.7 kg/m2). Treatment included insulin, but at the time of the report, the event was ongoing. Concomitant medications included clozapine (labeled for hyperglycemia and ketoacidosis) and Zyprexa (olanzapine; labeled for diabetes).

Comment: This patient was obese (obesity is a risk factor for diabetes). In addition, the patient was taking concomitant medications labeled for diabetes or DKA. Thus, it is difficult to demonstrate a clear causal role for Seroquel.

2001UW14447: This serious report of "Diabetic ketoacidosis" described a 13-year-old male patient who was receiving Seroquel (300 mg/day) for the treatment of bipolar disorder to control his fear, aggression, and mood swings. Once on Seroquel, the patient developed a "cardiac situation" that started with an arrhythmia and progressed to ischemia. A stress test revealed ischemia and the patient was scheduled for cardiac catheterization. Approximately

one month later, the patient was hospitalized for diabetic ketoacidosis and was discharged on insulin. The patient was in foster care and there was little information about family history, however, it was thought that there might be a family history of diabetes (several grandparents, mother). Medical history included morbid obesity. Concomitant medications included Depakote (valproate sodium; labeled for hyperglycemia). Additional information was requested.

Comment: This patient was obese (obesity is a risk factor for diabetes) and was taking a concomitant medication labeled for hyperglycemia. This patient may have had a positive family history for diabetes. Thus, it is difficult to demonstrate a clear causal role for Seroquel.

2001UW12263: This serious report of "Diabetic ketoacidosis" and "Hyperglycaemia NOS" described a 30-year-old male patient who had been receiving Seroquel (300 mg/day) for an unknown indication. The patient experienced abdominal pain, polydipsia, and polyuria. Later that month diabetic ketoacidosis and hyperglycemia occurred. Treatment included glyburide and insulin. Seroquel therapy was continued. Medical history was not provided. Concomitant medications included olanzapine (labeled for diabetic ketoacidosis).

Comment: This patient was taking a medication labeled for new onset diabetes mellitus and diabetic ketoacidosis. In addition, the report contained only minimal information making assessment difficult.

2001UW02143: This serious report of "Diabetic ketoacidosis" described a 48-year-old male patient who had been receiving Seroquel (dose unknown) for a few months for treatment of an unspecified psychiatric disorder. The patient experienced diabetic ketoacidosis. The patient "was on a day of leave and returned lethargic" (report did not specify if the patient was in a long term care setting). The patient was seen in the emergency room and his blood glucose was found to be 630 mg/dl and ketones were found in his urine; the patient was admitted to the hospital. Treatment included insulin and intravenous fluids. Laboratory results revealed a low-normal C-peptide (no value given) and Anti-GAD results were pending. Seroquel was continued for a day or two before the patient was switched to haloperidol. At the time of this report the patient's blood sugar was reported to be 250 mg/dl on insulin 70/30 2x/day. The patient was discharged from the hospital 13 days after admission. Medical history included hyperlipidemia. Concomitant medications included Ativan (lorazepam) and an unspecified "statin" medication.

Comment: This report does not mention if the patient had pre-existing diabetes or not. Hyperlipidemia is a risk factor for diabetes. This report described a negative dechallenge (that is the hyperglycemia did not resolve after Seroquel was discontinued. The scant clinical detail makes it difficult to assess.

2000UW02905: This serious report of "Diabetic ketoacidosis" described an 18-year-old patient (sex unknown) who had been receiving Seroquel (dose/duration/indication unknown). The patient was hospitalized with diabetic ketoacidosis, a blood sugar of 1200 (no units given), acute pancreatitis, and elevated lipids. Medical history was not provided.

Concomitant medications included sertraline (labeled for hyperglycemia). Outcome of events is unknown. Additional information has been requested.

Comment: This patient was receiving a medication labeled for hyperglycemia. In addition, because of the scant clinical detail, assessment is difficult.

2000UW01164: This serious report of "Diabetic ketoacidosis" described a 43-year-old male patient who had been receiving Seroquel (200 mg/day) for treatment of an unspecified mental illness. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 pounds. Fasting blood sugar showed glucose level over 700 (no units given). The patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. Seroquel therapy continued. Medical history was not provided. Concomitant medications included venlafaxine (labeled for hyperglycemia and diabetes mellitus). Outcome of the events is unknown. Additional information has been requested.

Comment: This report appears to described new onset diabetes in a patient taking a medication labeled for hyperglycemia and diabetes mellitus. Nonetheless, the minimal amount of information makes assessment difficult.

2000AP03612: This serious literature report of "Diabetic ketoacidosis" described a 64-year-old male patient with schizophrenia, who was switched from risperidone to Seroquel monotherapy (50 mg/day) 12 days after admission to the hospital (reason unknown). Seroquel was then increased to 100 mg in the morning and 300 mg at night. Two months later the patient was found unresponsive after breakfast and was transferred to a tertiary care center with a diagnosis of acute diabetic ketoacidosis. The patient was then lost to follow-up. The authors commented that the basal rate of diabetes mellitus in the Cincinnati area and among psychotic persons is higher than the national median. Medical history included chronic obstructive airways disease, prostate cancer, and diabetes mellitus. Concomitant medications included propranolol. Fasting blood sugar on an unknown date was 120 mg/dl.

Comment: This report did not contain information about what treatment measures this diabetic patient followed for the pre-existing diabetes. Assessment of causality is difficult due to scant clinical detail.

1999AP05757: This serious report of "Diabetic ketoacidosis" and "Diabetes mellitus NOS" described a 25-year-old male patient who had been receiving Seroquel (750 mg/day) for treatment of psychosis. One year and nine months after starting Seroquel the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (amount and date of onset unknown). Treatment with insulin was initiated and the patient recovered with residual side effects, and Seroquel therapy was continued. Medical history was not provided. Concomitant medications included Priadel (lithium; labeled for hyperglycemia), Depixol (flupenthixol; labeled for drug interaction with lithium - hyperglycemic reaction), and acamprosate.

Comment: This report is confounded with concomitant medications labeled for hyperglycemia. In addition, the weight gain could have triggered diabetes. Also, the scant clinical detail provided makes assessment difficult.

5.2.1.2 Reports of diabetic ketoacidosis with previous history of diabetes

2001UW05726: This serious report of "Diabetic ketoacidosis" described a 43-year-old male patient who had been receiving Seroquel (dose unknown) for the treatment of atypical psychosis. After six months of Seroquel therapy the patient died from possible diabetic ketoacidosis. Medical history included obesity, diabetes mellitus, Tourette's syndrome, borderline personality, and mild manic-depressive disorder. Concomitant medications included Haldol (haloperidol; labeled for drug interaction with lithium-hyperglycemic reaction), lithium (labeled for hyperglycemia), pimozide (labeled for drug interaction with lithium-hyperglycemic reaction), tetrabenazine, clonidine (labeled for hyperglycemia in NIDDM), Tegretol (carbamazepine), clomipramine, Ativan (lorazepam), clonazepam, propranolol, Zoladex (goserelin; labeled for hyperglycemia), chlorpromazine (labeled for hyperglycemia), and chloral hydrate. It was also noted that the patient had been on Risperdal at the same time that Seroquel was started; Risperdal was discontinued three to four months prior to the patient's death. The reporter also stated that the patient's lab values, in reference to diabetes, changed drastically (not indicated if they improved or worsened) once the patient started Seroquel (no values given). Additional information was requested.

Comments: It was unknown how well controlled the diabetes was prior to or during treatment with Seroquel. This report is confounded by multiple concomitant medications labeled for hyperglycemia. Thus, assessment of causality for Seroquel is difficult.

1998UW49554: This serious report of "Diabetic ketoacidosis" described a 58-year-old male patient who had been receiving Seroquel (800 mg/day; duration unknown) for the treatment of schizoaffective disorder. The patient experienced a transient ischemic attack (TIA) and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary cerebrovascular accident (CVA). Medical history included diabetes and CVA. Concomitant medications included gabapentin (labeled for diabetic ketoacidosis).

Comment: This patient had a history of diabetes and CVA, and was taking a medication labeled for diabetic ketoacidosis, thus confounding the report. The patient experienced a TIA followed the next day by a CVA and died. Significant medical illness can precipitate DKA. Therefore, it is difficult to assess causality to Seroquel.

2001UW16478: This serious report of "Diabetic ketoacidosis" (DKA) described a 32-year-old male patient who had received Seroquel (800 mg/day x 2 weeks) for the treatment of schizophrenia, mental retardation, and experienced diabetic ketoacidosis. Three days prior to the incident the patient complained of upper respiratory symptoms and dizziness. On the day of the event the patient had an episode of urinary incontinence, confusion, and abnormal heart rate. The blood glucose on chemstrip was abnormal (no value given). The peak glucose level

was 700 mg (no other unit). It was not reported whether Seroquel therapy continued. The patient remained hospitalized at the time of the report. Medical history included borderline diabetes (diet controlled). Concomitant medications included Risperdal (risperidone; labeled for diabetic ketoacidosis), Serentil (mesoridazine), Depakote (valproate; labeled for hyperglycemia), and Ativan (lorazepam). Additional information has been requested.

Comment: If the upper respiratory symptoms represented an infection, the infection could have precipitated DKA. This report is confounded with the use of concomitant medications labeled for DKA and hyperglycemia. Thus, assessment for a causal relationship to Seroquel is difficult.

2000AP04688: This serious report of "Diabetic ketoacidosis" described a 24-year-old male patient who had been receiving Seroquel (300 mg/day) for the treatment of schizophrenia. It was reported that the patient took five "ecstasy" tablets and then consumed an unknown amount of alcohol on a Saturday evening. The patient was admitted to the hospital on Sunday with nausea, vomiting, hypokalemia, metabolic acidosis and was treated for diabetic ketoacidosis. The patient was admitted to the high dependency unit with worsening renal function, increasing aggression, and possible aspiration pneumonia. He aspirated and was therefore intubated and transferred to the intensive care unit. The patient developed acute renal failure with increased creatinine levels, reaching a maximum of 327 umol/L (normal range = 55-150 umol/L) ten days after admission. Treatment included hemodiafiltration, and alfentanil, midazolam, propofol, haloperidol, epoprostenol, and metronidazole. Vancomycin and ciprofloxacin were initiated after methicillin-resistant Staphyloccocus aureus (MRSA) and coliform were identified. The acute renal failure resolved after two weeks and two days but the metabolic acidosis and hypokalemia were resolving slowly at the time of this report. The patient was unable to take his Seroquel and paroxetine after taking "ecstasy" due to the initial symptoms of nausea and vomiting. There is a possibility that the patient took an overdose of Seroquel but this was not confirmed. Follow-up information revealed that the patient was regularly prescribed Seroquel and paroxetine (labeled for hyperglycemia and diabetes mellitus) but his compliance was unknown. Medical history included insulin dependent diabetes mellitus, depression, and learning difficulties.

Comment: This report is confounded by alcohol consumption (alcohol can cause DKA), and concomitant medications labeled for hyperglycemia. Therefore, assessment of causality for Seroquel is difficult.

Summary of reports of diabetic ketoacidosis: Of the sixteen reports of DKA, 12 had no prior history or family history of diabetes reported. Three of these reports were confounded by both obesity (a known risk factor for diabetes mellitus) and the following concomitant medications: 2002GB01741 (nifedipine; labeled for hyperglycemia), 2002GB01254 (clozapine; labeled for hyperglycemia, olanzapine; labeled for diabetes mellitus), 2001UW14447 (Depakote; labeled for hyperglycemia). Another report (1999AP05757) was confounded by medications (lithium and Depixol) that are known to cause a hyperglycemic reaction when combined. Another report (2002UW08229) described a patient who died from DKA and diabetic renal failure, whereby the diabetic renal failure assumedly suggests some

degree of chronicity of the diabetes mellitus (although diabetes mellitus was not reported as part of the patient's medical history). This patient was also taking sertraline, which is labeled for hyperglycemia. Another report (2002UW09406) described a patient who took one single dose of Seroquel and experienced DKA. It seems unlikely that DKA could be causally related to a single dose of Seroquel.

The remaining six reports of DKA that had no prior history or family history of diabetes (2000AP03612, 2001UW12078, 2001UW12263, 2002UW02143, 2000UW02905, 2000UW01164) contained scant clinical detail and did not lend themselves to analysis. Also, four of these reports were confounded by the following concomitant medications: 2001UW12078 (Risperdal; labeled for DKA), 2001UW12263 (olanzapine; labeled for DKA), 2000UW02905 (sertraline; labeled for hyperglycemia), and 2000UW01164 (venlafaxine; labeled for hyperglycemia, diabetes mellitus).

The last four of the sixteen reports of DKA described patients who had pre-existing diabetes mellitus, and were confounded by the following medications: 1998UW49554 (gabapentin; labeled for diabetes mellitus, DKA), 2001UW16478 (Risperdal; labeled for DKA, Depakote; labeled for hyperglycemia), and 2000AP04688 (paroxetine; labeled for hyperglycemia, diabetes mellitus), and 2001UW05726 (Zoladex and chlorpromazine; labeled for hyperglycemia, Lithium; labeled for hyperglycemia and a drug interaction known to induce hyperglycemic reaction in combination with Haldol and/or pimozide). This last report was also confounded by obesity.

Following a review of these reports of DKA, it was determined that there is insufficient evidence to suggest a causal role for Seroquel and DKA.

5.2.2 Coma

Three reports of diabetic coma were identified. Two contained the MedDRA preferred term "Diabetic Coma NOS" and one contained the MedDRA preferred term "Nonketotic hyperglycaemic hyperosmolar coma". One of these report (2002AP01163) was received from Japan and is discussed in Section 6.1 above. The other two reports (2002UW05916, 2002GB02176) are discussed below.

5.2.2.1 Reports of coma with no previous history of diabetes reported

2002GB02176: This serious report of "Diabetic coma NOS" and "Diabetes mellitus insulin-dependent" described a female patient in her fifties who had been receiving Seroquel (no more than 400 mg/day) for an unknown indication. The patient developed type I diabetes and was admitted to the intensive care unit in a diabetic coma. The patient had received a combination of Lithium (lithium; labeled for hyperglycemia) and Seroquel for two years with no ill effect. During hospitalization, the patient was found to be hypernatremic, for which the reporter suspected Lithium. The patient was reported to have no history or family history of diabetes. At the time of this report the patient's condition was improving. No treatment measures, other medical history, or concomitant medications were provided. Additional information was requested.

Comment: This report had minimal information and did not lend itself to analysis. Also, the development of true type I diabetes is most often due to an autoimmune or an inherited disease. Furthermore, the report was confounded by a concomitant medication labeled for hyperglycemia.

2002UW05916: This serious report of "Nonketotic hyperglycaemic-hyperosmolar coma" and "Diabetes mellitus NOS" described a 12-year-old female patient who was receiving Seroquel while in a residential facility for nine months for treatment of behavior problems and aggression. One month prior to discharge, the dose of Seroquel was increased from 400 to 600 mg/day. Six days after discharge, the patient was hospitalized after experiencing a two-day history of mental status changes, polyuria, polydipsia, increased blood pressure, nausea, vomiting, abdominal pain, and sore throat. Blood glucose level was 1779 mg/dl. Abnormal lab tests included WBC = 18.3K, creatinine = 3.2 mg/dl, and BUN = 54 mg/dl. Plasma was negative for ketones. The patient was treated with potassium phosphate, cefotaxime, Versed (midazolam) for agitation, and Tylenol (acetaminophen). Despite the treatment, less than 12 hours later the patient became unconscious and died with a body temperature of 111°F. Cause of death was nonketotic hyperosmolar coma secondary to newly diagnosed diabetes mellitus. The patient also had an "unspecified" infectious process, which was felt to have precipitated the nonketotic hyperosmolar coma. An autopsy showed no evidence of infection, or any specific abnormalities other than the patient's height and weight. Medical history included mild mental retardation, seizure disorder, exceptionally tall and obese, and medical non-compliance (medical neglect). Concomitant medications included Celexa (citalopram; labeled for abnormal glucose tolerance), DDAVP (desmopressin), Ditropan (oxybutynin), and albuterol (labeled for hyperglycemia and DKA) .

Comment: This patient had a history of obesity (risk factor for diabetes) and medical neglect, and presented with a sore throat and an elevated WBC (indicative of an infection), which can all contribute to the development of new onset diabetes. In addition, this report is confounded by concomitant medications labeled for hyperglycemia. Thus, assessment for causality is difficult.

Summary of coma: Both reports of coma described new onset diabetes which can present itself as diabetic coma or non-ketotic hyperosmolar coma. Following a review of the reports of diabetic coma, it was determined that assessment of causality was difficult due to confounding by concomitant medications (2002GB02176: lithium; hyperglycemia, 2002UW05916: albuterol; DKA and hyperglycemia, citalopram; abnormal glucose tolerance). The evidence for causality regarding the use of Seroquel and diabetic coma was insufficient in these reports.

5.2.3 Other: Two reports with an outcome of death

Two reports not discussed elsewhere that contained an outcome of death were identified and are described below.

2002GB00282: This serious report of "Diabetes mellitus non-insulin dependent" described a 19-year-old male patient receiving Seroquel (dose and indication unknown) for approximately

four months when he developed type II diabetes mellitus. Four months later he died from an unknown cause, however, diabetes was suspected. The reporter did not consider Seroquel to be responsible for the patient's death. However, he suspected it might have been involved in the first expression of his diabetes taking the form of diabetic ketoacidosis. No further information was provided, however, additional information has been requested.

Comment: Assessment of causality is difficult due to minimal information.

1999UW00969: This serious report of "Diabetic complication NOS" described a 28-year-old male patient who had been receiving Seroquel (dose and duration unknown) for the treatment of schizophrenia. The patient presented to the emergency room with a temperature of 107°F, cardiac arrhythmias, focal twitching, increased tone, pupils were non-reactive, no reaction to noxious stimuli, bleeding from eyes and nose, liver enzymes twice normal (no values given), blood glucose 2240 (no units given), low potassium (no values given), CPK normal, and Lithium level was not elevated. There was no report of increase or decrease of body temperature before presentation. The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. Ativan (lorazepam), Dantrium (dantrolene), and anti-arrhythmics (unspecified) were started. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from onset. He died on hospital day two. A tentative diagnosis of NMS was made with complete autopsy reports pending. Medical history included bipolar disease, hallucinations, and asthma. Concomitant medications included albuterol (labeled for hyperglycemia and DKA), Eskalith (lithium; labeled for hyperglycemia), and Prilosec (omeprazole).

Follow-up information was received from the county coroner in the form of an autopsy final report and indicated the cause of death was complications of diabetes mellitus . The final findings were: 1) findings consistent with diabetes mellitus, 2) hepatomegaly with severe fatty metamorphosis, and 3) severe pulmonary congestion and hemorrhage. Comment from autopsy report: "This 28-year-old male died from multiple complications of a severe metabolic disorder of diabetic origin. He developed nonketotic hyperosmolar status which was followed by acidosis, hyperkalemia, hyperthermia, disseminated intravascular coagulation and cardiovascular instability." The autopsy report contained a clinical history as follows. "This patient was admitted to the hospital on the evening of 13 March 1999. He stayed in the hospital less than 12 hours and died on 14 March 1999. He was brought to the emergency room by ambulance, stuporous and with respiratory difficulty. He had a clinical history of mental disorder considered to be schizophrenia due to auditory hallucinations. His treatment included Depakote (divalproex) and Lithium (lithium), but the Depakote had been changed for Seroquel. He also had a history of asthma for which he used an albuterol inhaler. One week before the event the patient had flu-like symptoms and was seen by his primary doctor who prescribed Zithromax (azithromycin). However, he continued feeling poor, with progressive weakness until he collapsed in the bathroom. There was also a history of polydipsia, polyuria, and anorexia (10-15 lb. weight loss) for the three weeks prior to the event. On the day of admission the patient became confused. Upon admission the patient was febrile, dehydrated,

and had labored respirations without evidence of bronchial obstruction. He developed hypoxemia and required intubation. Intravenous fluids were given, chest x-ray was unremarkable, and drug screen showed only acetaminophen. Laboratory evaluation revealed severe acidosis with a pH of 7.19, potassium of 3.3, sodium of 114 (no units given), and a blood glucose of 2,200 mg/dL. Insulin treatment was started with the presumption of diabetic ketoacidosis, however ketones were not significantly elevated. The serum osmolality was 377 (no units). Body temperature increased as high as 109 °F and he required physical means for cooling. The possibility of NMS was entertained and dantrolene was started. Potassium determination indicated hypokalemia of less than 2 mEq/l and he received potassium chloride. Further complications occurred, with widening of the QRS complex on the EKG and apparent disseminated intravascular coagulation, evidenced by multiple sources of bleeding (unspecified). He was transfused with eight units of packed cells. Amiodarone was given for his wide complex tachycardia, but he continued worsening and arrested with ventricular fibrillation. He was defibrillated and converted temporarily. After several shocks, a pacemaker was installed due to profound bradycardia. After he arrested again and required defibrillation, it was requested that no further shocks were given. The patient was pronounced dead at 0400. The most important clinical diagnoses were: 1) new onset diabetes mellitus with nonketotic hyperosmolar coma, 2) malignant neuroleptic syndrome with hyperthermia, 3) metabolic acidosis and severe hypokalemia, 4) disseminated intravascular coagulation, 5) respiratory failure, 6) wide complex tachyarrhythmia." Additional information from the autopsy report included the following. The patient's height and weight were reported as 69 inches and 200 pounds, respectively. Autopsy showed the lungs to be heavy and markedly congested with generalized acute pulmonary congestion and areas of alveolar hemorrhage; liver to be bulky and markedly enlarged with the hepatic parenchyma showing fatty metamorphosis of microvesicular type involving approximately 90% of the hepatocytes and acute congestion with increased number of red cells in the sinusoid; spleen to be somewhat enlarged; and heart to have focal interstitial hemorrhage in sections from the right ventricle.

Comment: This report of previously undiagnosed diabetes presenting as non-ketotic hyperosmolar coma is consistent with an infection (fever, flu-like symptoms) precipitating the non-ketotic hyperosmolar coma. It is not unusual for an initial presentation of diabetes to be non-ketotic hyperosmolar coma or diabetic ketoacidosis precipitated by infection or some other significant medical illness. The patient's concomitant medications include albuterol, a β-2 agonist. β-2 agonists are well known to cause hyperglycemia. There have even been reports of diabetic ketoacidosis in patients receiving albuterol. The concomitant medication in this report also included lithium, which has been reported to be associated with hyperglycemia. The DIC is probably related to sepsis, and the arrhythmias, including the terminal ventricular fibrillation, were probably related to the acidosis, with a possible contribution by the β-2 agonist.

Summary of other reports: The first report had scant clinical detail. The second report was confounded by concomitant medications associated with hyperglycemia or even DKA. In addition, the second report presented a clinical picture consistent with infection precipitating the hyperosmolar coma. Thus, the evidence for causality regarding the use of Seroquel and diabetes is insufficient in these cases.

5.2.4 New Onset Diabetes Mellitus, Hyperglycemia, and Exacerbation of Diabetes

There are 60 reports divided into the following sections: 1.) new onset diabetes mellitus (29), 2.) hyperglycemia in patients with no prior history of diabetes (13), and 3.) exacerbation of diabetes (18). A summary for each section is presented

5.2.4.1 New onset Diabetes Mellitus

There were 29 reports of newly diagnosed diabetes mellitus. The demographic characteristics of these 29 reports were 14 male patients, 14 female patients and the gender was unknown in one report. There was no predominance in gender. The age range for these patients was 5 to 66 with a mean age at onset of 33 years (n = 22).

Of these reports, three patients developed insulin dependent diabetes mellitus (2001UW00363, 2001GB00094, 2000UW00266) which is considered not to be drug related and two patients (1999AP05218, 2002GB00947) developed gestational diabetes.

The reports of IDDM included the following reports: 2000UW00266, which described a 12-year-old patient who developed type I diabetes while receiving Seroquel, haldol, and valproic acid (labeled for hyperglycemia); 2001UW00363, which described a 5-year-old male patient with a family history of diabetes mellitus (grandfather) who was diagnosed after six month Seroquel therapy (12.5 to 37.5 mg/day); and 2001GB00094, which described 66-year-old patient was confounded by concomitant medication labeled for hyperglycemia (lithium).

The two reports of gestational diabetes described two female patients (age 27 and 32 years) who each developed diabetes during their pregnancies. The first report (1999AP05218) was confounded by concomitant medications labeled for diabetes (chlorpromazine and fluoxetine). The second report (2002GB00947) described a patient who was treated with olanzapine and then switched to Seroquel because of excessive weight gain. The patient become pregnant and developed gestational diabetes in the third trimester.

An additional 13 of these reports were confounded by concomitant medications labeled for hyperglycemia or diabetes. These reports and the relevant confounding medication(s) are listed below:

2002AP01607 (divalproex, paroxetine)

2002AP00323 (olanzapine, valproic acid, haloperidol)

2001UW13180 (fluoxetine; also a family history of diabetes mellitus)

2001UW07693 (prednisone)

2001UW00231 (mirtazapine, venlafaxine, also a history of blood glucose increased with Zyprexa)

2001SE07046 (mirtazapine)

2001AP03248 (mirtazapine)

2000UW02019 (lithium, venlafaxine, Ziac (bisoprolol/hydrochlorothiazide), also a family history (father) with diabetes mellitus)

2000AP05293 (venlafaxine, divalpoex)

1999UW00967 (Paxil (paroxetine), Depakote (valproic acid)

1999AP02989 (fluoxetine)

1999AP01985 (valproate)

1998UW48512 (lithium, venlafaxine)

Another three reports contained risk factors for diabetes: 2002GB01293 (family history of DM), 2001AP05019 (obesity), and 2000AP02609 (family history of DM).

Another six reports (2002UW03965, 2001UW13414, 2001SE08506, 2000UW04533, 2000UW04346, and 1998UW48844) contained scant clinical detail and did not lend themselves for analysis.

Another two reports described new onset-diabetes mellitus and are described below.

1999UW03532: This serious report of "Diabetes mellitus NOS" and "Weight increased" described a 47-year-old female patient receiving Seroquel (600 mg/day for 12 months) for schizoaffective disorder. She experienced a severe 50-pound weight gain (date of onset unknown) and developed diabetes mellitus. The patient was hospitalized in June 1999 and was difficult to control. Treatment included insulin and the patient's condition improved. Seroquel was tapered and discontinued. Concomitant medications included Klonopin (clonazepam) and Benadryl (diphenhydramine). The patient has a medical history of hepatitis C, hypertension, and arthritis. The diabetes continued.

1999UW03387: This nonserious report of "Diabetes mellitus non-insulin-dependent" described a 17-year-old Hispanic male patient receiving Seroquel (100 mg/day) since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime the dosage of Seroquel was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25 mg every evening. The patient had been receiving Risperdal (risperidone) prior to Seroquel. Concomitant medications include Ritalin (methylphenidate) for attention disorder and Serzone (nefazodone) for depression. Medical history included auditory hallucination, psychotic depression and attention disorder.

Summary of reports of new onset diabetes: Following a review of the reports describing patients who experienced new onset diabetes, it was determined that the available safety information was insufficient to establish a causal relationship between Seroquel and diabetes in these reports.

5.2.4.2 Hyperglycemia

There were 13 reports containing the MedDRA preferred term "Hyperglycaemia NOS" and "Blood glucose increased" which described patients that had no prior history of diabetes.

These reports involve seven male patients, two female patients, and four reports where the gender was not provided. The age (n = 6) ranged from 19 to 66 years (mean age = 44 years). The average dose was 418 (n = 7) with a range from 115 to 800 (excluding a report in which the patient overdosed on Seroquel (9600 mg). Blood glucose concentration at clinical presentation was provided in only three reports (2002UW11778, 2001UW02046, 1998AP50408) and were as follows: 7.1 (unit not specified), 12-20 (unit not specified) and 137 mg/dl, respectively.

Six of these reports were confounded by concomitant medications labeled for hyperglycemia or diabetes: 2002UW11778 (profenamine: hyperglycemia), 2002UW10490 (lisinopril/hydrochlorothiazide: hyperglycemia), 2002UW09743 (valproic acid: hyperglycemia. This report also is confounded with a family history of diabetes mellitus: brother, grandmother, aunt, and nephew), 2001SE02468 (mirtazapine: diabetes mellitus. This report also is confounded with the risk factor of obesity), 2001AP04330 (lithium: hyperglycemia), and 1998AP50408 (Stelazine (trifluoperazine: hyperglycemia).

Six reports (2002UW05977, 2002UW02227, 2002UW01476, 2001UW02046, 2001AP04437, 2000UW01047) contained scant clinical detail and did not lend themselves to analysis.

One literature report (1998UW49037) described a patient who took an overdose of Seroquel (9600 mg) and had "mildly elevated" serum glucose (137 mg/dl). No baseline glucose or concomitant medications were reported in this case.

Summary of reports of hyperglycemia: Following a review of all the reports of hyperglycemia, it was determined that assessment of causality was difficult because of confounding by concomitant medications and illnesses, or scant clinical detail. Thus, the evidence to establish a causal relationship for Seroquel and hyperglycemia was insufficient in these reports.

5.2.4.3 Exacerbation of Pre-existing Diabetes Mellitus

Ten reports containing the MedDRA preferred terms "Diabetes mellitus inadequate control", "Diabetes mellitus NOS", or "Diabetes mellitus aggravated" were identified, which described exacerbation of pre-existing diabetes mellitus. An additional eight reports involving patients with pre-existing diabetes, described only "Hyperglycaemia NOS" or "Blood glucose increased" without stating that there was an exacerbation of the diabetic status.

Of the reports describing an exacerbation of pre-existing diabetes mellitus, five were confounded by concomitant medications; 2002SE03085 (olanzapine; diabetes mellitus), 2002AP00855 (olanzapine; diabetes mellitus, fluoxetine; diabetes mellitus, and venlafaxine; diabetes mellitus and hyperglycemia), 2001GB00231 (beclomethasone oral inhalation and fluticasone nasal inhalation; both labeled for hyperglycemia), 2000AP04264 (olanzapine;

diabetes mellitus, fluoxetine; diabetes mellitus, and venlafaxine; diabetes mellitus and hyperglycemia), 2000UW04457 (nortriptyline: hyperglycemia).

Another four of the reports describing an exacerbation (2002UW12946, 2001UW08041, 2001UW07793, 1998AP45979) contained scant clinical detail and thus did not lend themselves to analysis. The remaining report describing an exacerbation is described below.

1999AP06660: This nonserious report of "Diabetes mellitus inadequate control" described a 45-year-old male patient who experienced a loss of diabetic control when Seroquel (300-400 mg x 5 months; increased to 750 mg/day) was initiated (particularly on the higher dose). Blood glucose increased from a stable level of 10 (units unknown) to 13 or greater. He was treated with glibenclamide (7.5mg/day). Medical history included schizophrenia and non-insulin dependent diabetes mellitus that had been initially treated with metformin and diet control. At the time of reporting, the patient was not yet recovered. No further information was provided.

Of the reports that described only "Hyperglycaemia NOS" or "Blood glucose increased" without stating that there was an exacerbation of the diabetic status, six of these reports were confounded by concomitant medications including; 2002UW08675 (bupropion; hyperglycemia), 2002SE05071 (phenytoin: hyperglycemia, rivastigmine hydrogen tartrate: precaution for use in diabetic patients), 2001AP04784 (olanzapine: hyperglycemia, diabetes mellitus, diabetic acidosis), 2002UW10887 (metoprolol labeled for hyperglycemia and for a drug interaction involving anti-diabetic drugs resulting in hyperglycemia), 2002UW08863 (Lipitor; atorvastatin: hyperglycemia, Zestril; lisinopril: labeled for diabetes), 2000UW04142 (Depakote; valproate semisodium: hyperglycemia),

Another case (2000UW03255) that did not actually report an exacerbation, described a 58-year-old diet controlled diabetic female patient who had been receiving Seroquel (300 mg day) for four months and experienced an elevated glucose level of 564 (no units). The patient was evaluated in the emergency room. The reporter physician stated that the "large amount of regular root beer ingested by the patient that day" could have caused the adverse event. Additional information has been requested.

The last case that did not actually report an exacerbation (1999UW00288) contained scant clinical detail and thus did not lend itself to analysis.

Summary of reports of exacerbation of pre-existing diabetes mellitus: Following a review of these reports of exacerbation of diabetes, and of hyperglycemia or increased blood glucose it was determined that assessment of causality was difficult in most cases because of confounding by concomitant medications, or scant clinical detail. In addition, two reports that described loss of diabetic control in patients with pre-existing diabetes are difficult to assess because there is no information about the patients situation which could disclose stressors contributing to glucose dysregulation. Another report described loss of diabetic control in a patient who drank large amounts of regular root beer the day the increased blood glucose level was identified. Thus, the evidence to establish a causal relationship for Seroquel and

exacerbation of diabetes (or hyperglycemia in patients with pre-existing diabetes) was insufficient in these reports.

5.2.5 Summary of reports from countries other than Japan

Following a careful review of all reports received from countries other than Japan, it was determined that assessment of causality was difficult in these cases because of either scant clinical detail, unclear temporal sequence of exposure and outcome, or confounding by concomitant medications and illnesses. None of these reports demonstrate a clear causal role for Seroquel and diabetes, DKA, or diabetic coma. The available safety information is insufficient to establish a causal relationship between Seroquel and glucose disorders. No changes to the Seroquel core data sheet are indicated at this time.

6. REVIEW OF LITERATURE

6.1 Search strategy

A thorough search of medical databases (including Medline, Embase, Biosis, Current Contents) through 02 October 2002 was conducted to obtain information on literature articles about diabetes in patients receiving Seroquel. In addition, the medical/scientific literature was searched for prevalence and incidence of diabetes in the schizophrenic patient population.

6.2 Search results

A summary of information obtained from the literature and database searches is provided below.

6.2.1 Prevalence in the schizophrenic population

Curkendall SM, Mo J, Jones JK, Glasser D. Increased cardiovascular disease in schizophrenia. World Journal of Biological Psychiatry 2001;2 Suppl 1:207S Abs P001-4.

This paper described a study designed to evaluate the prevalence and incidence of cardiovascular mortality and morbidity among 3022 schizophrenic patients and 12088 matched controls. The prevalence of arrhythmia, syncope, stroke, transient cerebral ischemia, **diabetes** and heart failure was significantly increased among the patients compared with the controls during 1994-1995. There was also a significantly increased relative risk for stroke, arrhythmia, **diabetes**, heart failure, nonsuicide mortality and cardiovascular mortality in patients compared with controls between January 1996-March 1999.

Dixon, L, Weiden, P, Delahanty, J, Goldberg, R, Postrado, L, Lucksted, A, and Lehman, A. Prevalence and Correlates of Diabetes in National Schizophrenia Samples. Schizophrenia Bulletin, Vol. 26 (4):903-912, 2000.

People with schizophrenia may be at increased risk for Type II diabetes because of the side effects of antipsychotic medication, poorer overall physical health, less healthy lifestyles, and poorer health care. The present study used databases collected by the Schizophrenia Patient

Outcomes Research Team (PORT) to assess the prevalence and demographic and clinical correlates of diabetes within large populations of persons receiving treatment for schizophrenia. In the Schizophrenia PORT, Medicaid and Medicare data from 1991 and more recent interview data were collected regarding the co morbidity of schizophrenia and diabetes: prevalence, quality of life, physical health, and services utilization and costs. The study found that rates of diagnosed diabetes exceeded general population statistics well before the widespread use of the new antipsychotic drugs. Risk factors for diabetes were similar to those observed in the general population. The linkage of diabetes to poor physical health, medical morbidity, and increased service use and cost requires attention. This study of diabetes in the early 1990's suggests that even before the widespread use of the atypical antipsychotic drugs, diabetes was a major problem for persons with schizophrenia.

Mukherjee S, Decina P, Bocola V, Saraceni F, Schapicchio PL. Diabetes Mellitus in Schizophrenic Patients. Comprehensive Psychiatry 1996;7(1):68-73

Studies conducted in the United States and Japan indicate that diabetes mellitus is more common among schizophrenic patients than among the general population. The prevalence of known diabetes was examined in 95 schizophrenic patients aged 45 to 74 years admitted to long-term care facility in Italy. The overall prevalence of diabetes was 15.8% (95% confidence interval, 12.1% to 19.5%), and increased from 0% in those younger than 50 years, though 12.9% in the 50- to 59-year group, and to 18.9% in the 60- to 69- year age group, and then decreased to 16.7% in those aged 70 to 74 years. These rates are considerably higher than those reported from population surveys in Italy, and indicate that a higher prevalence of diabetes in schizophrenic patients may be a universal phenomenon. The clinical picture indicated that in all cases this was the common variant of type II (non-insulin-dependent) diabetes mellitus. Diabetes was more common in patients not receiving neuroleptics than in those who were receiving such treatment. There was no association between diabetes and the use of anticholinergic drugs

6.2.2 Diabetes and Antipsychotic Treatment

Gianfrancesco F, White RE, Yu E. NR 400: antipsychotics-induced type 2 diabetes: evidence from a large health plan database. Presented at the annual meeting of the American Psychiatric Association—Institute on Psychiatric Services, Chicago, IL, October 10, 2002.

This abstract described a retrospective study designed to evaluate the association of antipsychotic treatment with type II diabetes in a large health plan database. Analysis of claims data for patients with psychosis within a health plan of nearly two million patients were analyzed. Frequencies of newly treated type II diabetes in patients untreated with antipsychotics and among patients treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics were compared. Based on exposure measured in months of antipsychotic treatment, risperidone and quetiapine patients had estimated odds of receiving treatment for type II diabetes that were lower than those of patients untreated with antipsychotics (not statistically significant); conventional antipsychotics had estimated odds that were virtually equivalent to those of patients untreated with antipsychotics; olanzapine

alone had odds that were significantly greater than those of patients untreated with antipsychotics (P<0.05). Odds ratios based on eight months of prescreening for preexisting type between antipsychotics and type 2 diabetes and assuming 12 months of antipsychotic treatment were: risperidone=0.652 (95% CI, 0.306–1.393); olanzapine=1.426 (95% CI, 1.049–1.945); quetiapine=0.953 (95% CI, 0.408–2.227); and conventional antipsychotics=1.024 (95% CI, 0.669–1.564). The authors stated that this large population study confirms case report findings that have increasingly implicated olanzapine as causing or exacerbating type II diabetes, (while few have implicated quetiapine and risperidone). In this study, patients treated with olanzapine alone were shown to face higher odds of type II diabetes than patients with psychosis untreated with antipsychotics. In contrast, quetiapine and risperidone had estimated odds that were less than those of untreated patients, although this difference was not statistically significant. The authors concluded that with regard to the risk of type II diabetes, these atypical antipsychotics appear to be safer than olanzapine.

Michael J. Sernyak, Douglas L. Leslie, Renato D. Alarcon, Miklos F. Losonczy, Robert Rosenheck. Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia. Am J Psychiatry 2002; 159:561–566.

This paper discussed a retrospective study designed to compare the prevalence of diabetes mellitus in patients receiving prescriptions for atypical and typical neuroleptics. A total of 38,632 patients, all outpatients with schizophrenia over four months in 1999 in the Veterans Health Administration, were included in the study. The number of patient receiving typical neuroleptics was 15,984 (41.4%) and those receiving any atypical neuroleptics was 22,648 (58.6%). The breakdown of the atypical neuroleptics is as follows; patients receiving clozapine (1,207: 5.3%); olanzapine (10,970: 48.4%), quetiapine (955: 4.2%), and risperidone (9,903: 43.7%). In addition, 387 patients received prescriptions for more than one atypical neuroleptic. The authors concluded that when the effects of age were controlled for, patients who received atypical neuroleptics were 9% more likely to have diabetes than those who received typical neuroleptics, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone. However, for patients less than 40 years old, all of the atypical neuroleptics were associated with a significantly increased prevalence of diabetes. The authors identified several limitations of this study, including the following: 1.) the populations were significantly different in age, sex, presence of other psychiatric diagnosis(s), economic status, distance from medical care, and inpatient/outpatient status, 2.) the narrow time frame (four months) yielded a virtual cross-sectional sample, precluding determination of the temporal relationship between the prescription of neuroleptics and the development of diabetes mellitus, 3.) data on changes in weight gain (one potential mechanism of action for the development of diabetes) were unavailable, 4.) the patients who received typical neuroleptics may have been less likely to take the medication because of their side effect profile, 5.) it is possible that patients with pre-existing diabetes were selectively switched to atypical neuroleptics, or that clinicians chose to monitor blood sugars more carefully in patients taking atypical neuroleptics, thereby identifying additional cases of diabetes and inflating the effect size. The authors theorized that it is possible that both atypical neuroleptic prescription and receipt of a diagnosis of diabetes could be associated with more severe forms of schizophrenia. Lastly, the authors

concluded that although this study demonstrated a substantial and statistically significant association between atypical neuroleptic prescription and diabetes, it did not definitively establish a causal relationship.

Casey DE. Atypical antipsychotics: Enhancing healthy outcomes. Archives of Psychiatric Nursing 2002;16(3) Suppl 1:S12-9.

This article discussed the prevalence of risk factors for cardiovascular disease in schizophrenia, and the influence of some antipsychotics on obesity, diabetes and hyperlipidemia. It is mentioned that the effect of quetiapine on weight peaks after almost 2 months and then stabilizes. It is also mentioned that a recent study estimated that the prevalence rate of diabetes mellitus in quetiapine treated patients was 12%, which represents only diagnosed cases. It is finally noted that several brief reports suggest that quetiapine, clozapine, olanzapine and risperidone elevate cholesterol or triglycerides in some patients.

Meltzer HY. Putting metabolic side effects into perspective: Risks versus benefits of atypical antipsychotics. Journal of Clinical Psychiatry 2001;62 Suppl 27:35-9.

The lengthy list of the side effects and morbidity associated with the atypical antipsychotics might make a patient with psychosis and his or her caregivers so concerned about the use of any of these medications, particularly those associated with a higher risk of diabetes, weight gain, or increased lipid levels, that they would prefer to avoid all of them. However, schizophrenia is associated with a relatively high risk for several diseases, including diabetes, that is independent of the risks that are linked to atypical antipsychotic use. Therefore, the clinician, who might think "Why use atypicals if using the typical drugs will escape the problems of monitoring and all the associated effects of diabetes and hyperglycemia?" needs to know that these problems cannot be avoided simply by choosing typical antipsychotics. Clinicians, patients, and concerned family members must balance the significant benefits of atypical antipsychotic treatment-improved cognition, reduced suicidality, and less depression-against the risks of metabolic disturbances and select a course of treatment that includes a realistic monitoring program.

Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. Journal of Clinical Psychiatry 2001;62 Suppl 27:15-26.

Type II diabetes mellitus and impaired glucose tolerance are associated with antipsychotic treatment. Risk factors for type II diabetes and impaired glucose tolerance include abdominal adiposity, age, ethnic status, and certain neuropsychiatric conditions. While impaired glucose metabolism was first described in psychotic patients prior to the introduction of antipsychotic medications, treatment with antipsychotic medications is associated with impaired glucose metabolism, exacerbation of existing type I and II diabetes, new-onset type II diabetes mellitus, and diabetic ketoacidosis, a severe and potentially fatal metabolic complication. The strength of the association between antipsychotics and diabetes varies across individual medications, with the largest number of reports for chlorpromazine, clozapine, and olanzapine. Recent controlled studies suggest that antipsychotics can impair glucose regulation by decreasing insulin action, although effects on insulin secretion are not ruled out.

Antipsychotic medications induce weight gain, and the potential for weight gain varies across individual agents with larger effects observed again for agents like chlorpromazine, clozapine, and olanzapine. Increased abdominal adiposity may explain some treatment-related changes in glucose metabolism. However, case reports and recent controlled studies suggest that clozapine and olanzapine treatment may also be associated with adverse effects on glucose metabolism independent of adiposity. Dyslipidemia is a feature of type II diabetes, and antipsychotics such as clozapine and olanzapine have also been associated with hypertriglyceridemia, with agents such as haloperidol, risperidone, and ziprasidone associated with reductions in plasma triglycerides. Diabetes mellitus is associated with increased morbidity and mortality due to both acute (e.g., diabetic ketoacidosis) and long-term (e.g., cardiovascular disease) complications. A progressive relationship between plasma glucose levels and cardiovascular risk (e.g., myocardial infarction, stroke) begins at glucose levels that are well below diabetic or "impaired" thresholds. Increased adiposity and dyslipidemia are additional, independent risk factors for cardiovascular morbidity and mortality. Patients with schizophrenia suffer increased mortality due to cardiovascular disease, with presumed contributions from a number of modifiable risk factors (e.g., smoking, sedentary lifestyle, poor diet, obesity, hyperglycemia, and dyslipidemia). Patients taking antipsychotic medications should undergo regular monitoring of weight and plasma glucose and lipids levels, so that clinicians can individualize treatment decisions and reduce iatrogenic contributions to morbidity and mortality.

Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. Journal of Clinical Psychiatry 2001;62 Suppl 23:30-8.

The available literature suggests that patients with schizophrenia are at risk for diabetes mellitus and taking antipsychotic medication further increases the chance of developing non-insulin-dependent hyperglycemia. Case reports, chart reviews, and some results from clinical drug trials implicate a relationship between glucose levels and treatment with clozapine or olanzapine in patients with schizophrenia, although a few cases of hyperglycemia have also been reported in patients taking risperidone and quetiapine. These studies indicate that hyperglycemia is not dose dependent, is reversible on cessation of treatment with clozapine or olanzapine, and reappears on reintroduction of these therapies. The postulated underlying mechanisms involved in this process in patients with schizophrenia include (1) a decreased sensitivity to insulin that is independent of atypical medication, (2) an increased insulin resistance related to atypical medications, (3) the effects of atypical medications on serotonin receptors, and (4) overuse of insulin due to weight gain. These mechanisms are discussed in detail and recommendations for the administration of atypical antipsychotics are offered. Overweight, ethnicity, family or personal history of diabetes mellitus or hypertension, and weight gain during the course of treatment have all been identified as risk factors in the development of hyperglycemia in patients with schizophrenia. However, it is difficult to statistically assess the true incidence of diabetes within each type of antipsychotic medication group with the exclusive dependence on available case studies and without proper epidemiologic research.

Cohn T, Remington G. Changing times, changing concerns-a cross-sectional study of antipsychotic medication use and cardiac risk factors in 213 long-term psychiatric inpatients. International Journal of Neuropsychopharmacology 2000;3 Suppl:S153, Abs P.01.225.

A profile of antipsychotic use was obtained from 213 psychiatric inpatients (mean age 46 years) with schizophrenia, and the cardiac risk factors associated with antipsychotic use were evaluated. The patients were taking mean doses of clozapine 403 mg/day (n = 68), olanzapine 15.5 mg/bid (n = 57), depot zuclopenthixol 396 mg/day (n = 43), risperidone 4.6 mg/day (n = 24), quetiapine 395 mg/day (n = 20) or other antipsychotics (n = 41). Seventy percent of the patients smoked in comparison with 30% of the general population. Sixty percent of the patients had a body mass index > 27 in comparison with 30% of the general population. Eighteen percent gained > 25% of their body weight, 49% gained > 5% body weight, 38% gained or lost < 5% body weight and 13% lost > 5% body weight from the time of admission. Men comprised 60% of the weight gain group and women comprised 60% of the weight loss group. Thirty-five percent of the patients exhibited triglyceride levels > 2.3 compared with 15% of the general population. There were no cases of hypertriglyceridemia in quetiapine patients. There were no significant differences between schizophrenia patients and the general population in cholesterol, HDL or LDL levels. There were no cases of diabetes in quetiapine patients, and the incidence of diabetes in other patients exceeded that of the general population. The authors conclude that long-term psychiatric patients on antipsychotics have increased rates of smoking, obesity, hypertriglyceridemia and diabetes in comparison with the general population and note that this puts them at an increased risk for developing coronary artery disease and other obesity-related complications.

6.2.3 Weight gain related to incidence of diabetes and hyperglycemia

Ryan MCM, Thakore JH. Physical consequences of schizophrenia and its treatment – The metabolic syndrome. Life Sciences 2002;71(3):239-57.

Schizophrenia is a life shortening illness. In this paper, both unnatural and natural causes are put forward as reasons for this excess mortality. Different physical disorders such as type II diabetes mellitus and cardiovascular disease occur with increased frequency in schizophrenia, and thus lead to increased morbidity and mortality. When taken together, some of these illnesses (such as type II diabetes mellitus and cardiovascular disorders) constitute the Metabolic Syndrome; a characteristic phenotype of those with this syndrome is excessive visceral fat distribution. The exact reasons why this particular syndrome occurs in schizophrenia is as yet unclear though factors such as lifestyle, poor diet, and lack of exercise may contribute to its development. Alternatively, the authors suggested that overactivity of the hypothalamic-pituitary-adrenal axis leading to hypercortisolaemia can also result in excessive visceral fat accumulation.

Chue PS. Are atypical antipsychotics associated with an increased risk of diabetes, and is this associated with weight gain?. Journal of Psychiatry and Neuroscience 2001;26(4):360.

This paper discussed whether atypical antipsychotics are associated with an increased risk of diabetes, and whether this is associated with weight gain. The authors concluded that studies have reported significantly greater impairment on indices of insulin resistance and glucose regulation with olanzapine and clozapine than with quetiapine, risperidone, and ziprasidone.

Russel JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics – Epidemiology and therapeutic implications. CNS Drugs 2001;15(7):537-51.

The main focus of this review was the gain in bodyweight associated with the use of atypical antipsychotics and the impact on quality of life and medical comorbidity, which results from this bodyweight gain. Quetiapine is among the drugs reviewed which has been linked to a gain in bodyweight and other antipsychotics discussed include clozapine, risperidone, olanzapine, ziprasidone, zotepine and amisulpride. Of the few studies, which have assessed the effects of quetiapine on weight gain, one short-term trial demonstrated that 25% of quetiapine-treated patients experienced clinically significant weight gain compared to only 4% of patients who received placebo. There was an increase of 0.09-5.5 kg after treatment duration of 4-8 weeks and after one year a mean increase in bodyweight of 2.2 kg and 5.6 kg was reported. Another comparative study showed that 16% of quetiapine-treated patients experienced an increase in bodyweight of >= 7% of baseline compared to 4% of haloperidol-treated patients and 6% of those who received placebo. However, a third study showed a total bodyweight loss of 0.45-18.6 kg in schizophrenia patients initially treated with clozapine for six months followed by treatment with a combination of clozapine and quetiapine for 10 months. The mechanisms of atypical antipsychotic-associated bodyweight gain are likely multifactorial and may include a reduction in basal metabolic rate as a result of sedation, reduced caloric utilization and increased thirst and appetite due to anticholinergic effects. Those patients at a greater risk from bodyweight gain include those with a low body mass index prior to treatment, younger patients and female patients. The particular psychiatric condition and the use of mood stabilizers are also factors. An increase in bodyweight gain increases the risk of developing diabetes mellitus and cardiovascular disease as well as being detrimental to the patient's quality of life. However, there is evidence to suggest that when quetiapine is added to clozapine therapy there is an improvement in diabetes mellitus, as shown in three of 13 patients receiving this therapy. Overall, the authors concluded that it is very important that psychiatrists monitor their patients closely given the increase in obesity-related comorbidities and cardiovascular risk factors associated with the use of atypical antipsychotics and that prevention and management of bodyweight are vital.

Anonymous. Atypical antipsychotics and bodyweight gain: how serious is the problem?. Drugs & Therapy Perspectives 2002;18(8):23-6.

Bodyweight gain is a relatively common adverse effect associated with atypical antipsychotic drugs, although the propensity to cause this problem appears to vary between the specific agents. Available data indicate that clozapine and olanzapine are associated with more bodyweight gain than other atypical antipsychotics, but various methodologies have been used to collect this information in clinical trials and there are few direct comparative studies. While there is no consensus on the definition of a clinically significant increase in

bodyweight, a review of clinical trials with clozapine found that 27 to 70% of patients treated for four to 24 months had bodyweight gains greater than or equal to10% of baseline bodyweight, and mean increases ranged from 2.3 to 16.2kg. Olanzapine was associated with gains of 1.9 to 11.8 kg in clinical trials of varying duration. Bodyweight gain induced by atypical antipsychotic drugs can be a serious, and often long-term, adverse effect potentially leading to noncompliance with therapy (and therefore relapse), as well as comorbidities such as diabetes mellitus and coronary artery disease. However, the potential risks associated with bodyweight gain should not be the only factor in drug selection for patients requiring antipsychotic therapy, as clinical response and the incidence of other adverse events must also be considered

6.2.4 Quetiapine/Clozapine combination

Reinstein MJ, Sirotovskaya LA, Jones LE, Mohan S, Chasanov MA. Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control: Preliminary Findings. Clinical Drug Investigation 1999;18(2):99-104.

Data on body weight changes and diabetes status were collected from an open-label, non-randomized, 10-month, retrospective, comparative study, by reviewing the charts of 65 schizophrenic patients, initially treated with clozapine for six months and then switched to clozapine-quetiapine combination therapy. Clozapine doses were 200-800 mg/day that were tapered up to 25% of the current dose, and quetiapine added proportionally (1 mg clozapine substituted for 2 mg quetiapine); quetiapine doses were 200-800 mg/day. Diabetic status was assessed for those patients who had developed diabetes whilst taking clozapine monotherapy (n = 13) and weight was recorded monthly. All patients showed weight loss with a mean loss of 3.98 pounds in the first month, and 9.2 pounds over the 10-month study period. Twenty percent of those patients who developed diabetes with clozapine monotherapy showed significant improvement with the addition of quetiapine. There were no significant adverse events and compliance with therapy was 100%. The most common adverse event was drowsiness. The authors concluded that quetiapine shows an unusual propensity to induce weight loss and helps manage the diabetes that may develop during clozapine monotherapy. They further concluded that the data supports the safety and tolerability of clozapine-quetiapine combination therapy.

Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. European Neuropsychopharmacology 2001;11(1):25-32.

This article examined emerging evidence that suggests the onset of diabetes mellitus (DM) may be associated with atypical antipsychotic agents, such as clozapine and olanzapine and possibly quetiapine. There has been one reported case of quetiapine-induced diabetes in a white male (aged 42 years). Prior to developing DM the patient who had no case history of DM, was taking Seroque (200 mg/night) for one month. The dose of quetiapine was subsequently decreased and discontinued over nine days and patient's hyperglycemic symptoms were resolved over five months. This paper discussed an open-label, non-randomized, retrospective study designed to assess changes in weight and DM status for patients (n = 65) initially treated with clozapine who developed DM and then switched to

clozapine-quetiapine combination therapy over a 10-month period. At the initiation of quetiapine therapy patient's clozapine doses ranged from 200-800 mg/day. The clozapine dose was reduced by up to 25 % and quetiapine was added proportionally: 1 mg clozapine was substituted for 2 mg of quetiapine. Daily doses of quetiapine ranged from 200-800 mg/day. The combination therapy of clozapine-quetiapine produced significant weight loss and improvement in DM status. Serum glycosylated hemoglobin A (HgbA1) and glucose levels had returned to normal by the end of the study. The authors concluded that quetiapine induced weight loss and improved glycemic control in patients that gained weight and developed DM on clozapine. They also demonstrated that clozapine and quetiapine could safely be given in combination without added side effects, as drowsiness was the most common adverse event reported.

6.3 Conclusion

The literature reveals that schizophrenic patients are at a higher risk for developing diabetes mellitus given the risk factors that are commonly seen in this patient population (ie. hypertension, obesity, smoking, sedentary lifestyle, poor diet, and dyslipidemia). The literature consistently showed an association between diabetes mellitus and olanzapine and clozapine, but not the other atypical antipsychotics.

There were two large retrospective studies conducted to evaluate the relationship between diabetes and antipsychotic medications. Gianfrancesco et al. 2002 showed an association between diabetes and olanzapine, but not quetiapine or risperidone. The other retrospective study (Sernyak et al. 2002) showed an association between diabetes and clozapine, olanzapine, and quetiapine compared to typical antipsychotics but acknowledged limitations of the study that could have confounded the results.

An open-label, non-randomized, retrospective study conducted to assess changes in weight and diabetes mellitus status for patients initially treated with clozapine who developed diabetes and then switched to clozapine-quetiapine combination therapy (over a 10 month period) demonstrated that quetiapine induced weight loss and improved glycemic control in those patients that gained weight and had developed diabetes on clozapine.

7. OVERALL CONCLUSION

Through 31 July 2002, there have been an estimated four million Seroquel patient exposures worldwide. Given this exposure, the number of postmarketing reports of glucose dysregulation in patients using Seroquel is very small. There is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. The majority of reports of diabetes mellitus did not include baseline fasting blood glucose levels to rule-out preexisting disease in new-onset diabetics or to indicate the degree of glycemic control in patients with preexisting diabetes. Regarding the latter cohort, patients with schizophrenia are frequently noncompliant with treatment regimens including medications and lifestyle modifications used to achieve glycemic control. This position is also supported by the literature where the

incidence of diabetes mellitus in the schizophrenic population is noted to exceed that in the general population, even prior to the introduction of atypical antipsychotic medications (Dixon et al 2000).

Following a careful review of all diabetes related reports received from both Japan and all other countries, it was determined that assessment of causality was difficult in these cases because of either scant clinical detail, unclear temporal sequence of exposure and outcome, or confounding by concomitant medications and illnesses. Following a review of all the available relevant pre-clinical, clinical and safety information, as well as the medical/scientific literature, it was determined there is insufficient evidence to establish a causal relationship between Seroquel and glucose disorders.

Therefore, it is concluded that that no changes to the Seroquel core data sheet are indicated at this time. AstraZeneca will continue to keep reports of diabetes mellitus and related disorders under careful review.