EXHIBIT 26

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CN : SQ1ED00428632
Date : Tuesday, October 31, 2000 7:20:00 AM GMT
From : Witch, Emma
To : Haas, Edward J
Cc : Geller, Wayne
Subject : RE: Urgent--Request for Seroquel document re Diabetes sent to FDA
Attachments : final document 280800.doc
Custodians : Geller, Wayne

From:
Witch, Emma

Sent:
Tuesday, October 31, 2000 8:25 AM

To:
Haas, Edward J

Cc:
Geller, Wayne

Subject:
RE: Urgent--Request for Seroquel document re Diabetes sent to FDA

Attachments:
final diabetes document 280800

Hi there

CONFIDENTIAL

Here is the diabetes doc that went to the FDA.

Regards

Emma

From: Haas, Edward J

Sent: 30 October 2000 22:50

To: Witch, Emma

Cc: Geller, Wayne

Subject: Urgent--Request for Seroquel document re Diabetes sent to FDA

Hello Emma,

Can you please provide me and Wayne wth a copy of the document that was sent to the FDA regarding diabetes. Thank you very much!

Ed

cid:CHILKAT-CID-469c0a8d-8b33-4364-90d9-a7d90f0ecb84

SEROQUEL™ (quetiapine fumarate)

Response to FDA request for further safety information

To assess the possibility of a causal association between Seroquel treatment and disturbances in glucose regulation

NDA 20-639

August 2000

CONTENTS PAGE

1 INTRODUCTION

The purpose of this document is to provide the FDA with further safety information in order to assess whether there is a causal association between Seroquel treatment and disturbances in glucose regulation, in particular the onset of diabetes.

The FDA have requested 6 pieces of information; these are summarized as follows:

(1) A comprehensive review of all preclinical data pertaining to hyperglycemia.

(2) A thorough assessment of all Phase 1, 2 and 3 studies in the Seroquel NDA for evidence of adverse events possibly related to disturbances in glucose regulation, mean changes from baseline in plasma glucose levels, and the number of patients meeting the criteria for a markedly abnormal plasma glucose concentration.

(3) A review of spontaneous postmarketing reports for new-onset diabetes, hyperosmolar coma, diabetic ketoacidosis, weight gain and hyperglycemia.

(4) An estimate of patient exposure.

(5) Copies of any correspondence with regulatory authorities regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

(6) The possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

AstraZeneca has now collated and thoroughly assessed all the appropriate data to address each of the above, and full details are provided in this document (Sections 4 to 9).

A summary of preclinical, clinical and postmarketing findings, and an overall conclusion, is provided overleaf.

2 SUMMARY OF DATA

Preclinical data

- A review of all the preclinical data has confirmed that the only salient observations are small changes in glucagon secreting cells in a 1-year rat study with quetiapine fumarate.

  No such changes were observed after administration of quetiapine fumarate at the same dose levels for 2 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.

  Overall it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

Clinical data

- The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies and, after adjusting for time-on-study, the incidence of these events did not increase as the duration of exposure to Seroquel increased:
  - cumulative incidence: 1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials (≤ 6 weeks duration), 4.6% in the long-term controlled (> 6 weeks duration) and 3.6% in the uncontrolled trials.
  - incidence density (events/patient-years): 0.6 in the Phase I trials, 0.2 in the short-term controlled trials, 0.2 in the long-term controlled trials and 0.1 in the uncontrolled trials.
- None of the 2419 patients exposed to Seroquel in the clinical trial program were reported as having diabetic ketoacidosis or hyperosmolar coma.
- Only 3 of 2419 patients (0.1%) were reported as having diabetes mellitus (all in the uncontrolled trials). In 2 of the 3 cases, the patients had a past history of diabetes. In the third case, the patient is reported to have 'recovered' from diabetes and continued treatment with Seroquel.

- The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (67 of 2419 patients, 2.8%).

Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program also had diabetes mellitus recorded as an adverse event. This patient had diabetes at baseline (for which they were receiving treatment) and the adverse event of 'poorly controlled diabetes' was subsequently reported.

- There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due to events possibly related to glucose dysregulation; details are as follows:

  - 2 patients were withdrawn for hyperglycemia in the uncontrolled trials. In both cases, the hyperglycemia was considered serious by the Investigator. Both patients had baseline confounding factors: 1 was a known diabetic with a history of hyperglycemia and 1 had a history of borderline glucose levels.

  - 1 patient was withdrawn for weight gain in the short-term controlled trials. The weight gain was not considered serious by the Investigator. Somnolence and abdominal distension were also documented as reasons for withdrawal from treatment in this patient.

  Apart from the 2 adverse events of hyperglycemia above, none of the other events possibly related to disturbances in glucose regulation in the NDA clinical trial program were considered serious by the Investigator.

- There were no statistically significant differences between the Seroquel and placebo groups, Seroquel and chlorpromazine groups (short-term trials) or Seroquel and haloperidol groups (long-term trials) in the mean change from baseline to end of treatment in plasma glucose levels.

- The number of patients treated with Seroquel with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (3.4% in the short-term trials [≤ 6 weeks duration] and 2.9% in the long-term trials [> 6 weeks duration]).

- Where hyperglycemia was observed (glucose value ≥ 200 mg/dl), the condition was not sustained or extreme, and the patients were asymptomatic.

Postmarketing data

- It is estimated that over 623,000 patients have been exposed to Seroquel since its launch in the US in 1997. During this time:
  - no cases of hyperosmolar coma have been reported.
  - 3 cases of diabetic ketoacidosis have been reported. In 2 cases, usage of concomitant medications known to impair glucose tolerance was noted.
  - 12 cases of new-onset diabetes have been reported. In 6 patients, usage of concomitant medications known to impair glucose tolerance was noted.
  - 2 cases of hyperglycemia have been reported.
  - 38 cases of weight gain were reported. Only 2 of the 38 patients with weight gain also had diabetes mellitus.

  Thus very few cases of diabetes mellitus (and related complications), hyperglycemia, and weight gain have been reported. AstraZeneca believes that the current US Seroquel label accurately describes patient experiences to date of these conditions.

3 CONCLUSION

The preclinical data has provided no evidence that Seroquel treatment in man may be associated with diabetes.

The clinical data has shown that the incidence of adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel is low and does not increase as duration of exposure to Seroquel increases. Very few of the adverse events observed were considered serious or led to withdrawal of treatment. There were no cases of diabetic ketoacidosis or hyperosmolar coma and only 3 cases of diabetes mellitus were reported.

A review of the plasma glucose data has revealed similar findings: the hyperglycemia (glucose value ≥ 200 mg/dl) observed in a small number of patients treated with Seroquel 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.

The postmarketing data has shown that even though over 600,000 patients are estimated to have received Seroquel, the number of reported cases of diabetes and related conditions has been extremely small.

Overall, following extensive reviews of all the preclinical, clinical, and postmarketing data, AstraZeneca believes that a diabetogenic potential for Seroquel is unlikely.

4 REVIEW OF PRECLINICAL DATA

In response to Part 1 of the FDA's request, AstraZeneca has completed a comprehensive review of all the preclinical data for evidence of an association between quetiapine fumarate treatment and disturbances in glucose metabolism.

4.1 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 2 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 fumarate. 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.

4.2 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 fumarate 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 was 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.

4.3 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 1-year rat study with quetiapine fumarate. 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.

5 REVIEW OF CLINICAL DATA

In response to Part 2 of the FDA's request, AstraZeneca has thoroughly reviewed the clinical safety database in the Seroquel NDA for evidence of an association between Seroquel treatment and disturbances in glucose metabolism.

5.1 Source material

5.1.1 Adverse event data

In the Seroquel NDA, adverse events were categorized 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 be related to disturbances in glucose metabolism has been identified, and are as follows:

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

The incidence of the above events in all of the patients in the Seroquel NDA clinical trial program has been reviewed and assessed in this report. The number of patients exposed to treatment in the Seroquel NDA clinical trial program is presented in Table 1.

Table 1 Summary of clinical trials in the Seroquel NDA integrated database

Pools by trial design	Treatment group and number of patients			
	Seroquel	Placebo	Haloperidol	Chlorpromazine
Phase I	300	0	0	0
Controlled Phase II/III	1710	206	320	100
Short-term (≤ 6 weeks duration)	1450	206	279	100
Long-term (> 6 weeks duration)	260	0	41	0
Uncontrolled	1256	0	0	0
New exposures	409	0	0	0
Patients already counted under previous headings[a]	847	0	0	0
All trials	**2419**	**206**	**320**	**100**

[a] Previously took part in Phase I or controlled Phase II/III trials

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

- Phase I trials
  (Seroquel; N=300)
- Short-term controlled Phase II/III trials
  (≤ 6 weeks duration: Seroquel; N=1450, placebo; N=206, haloperidol; N=279, chlorpromazine; N=100)
- Long-term controlled Phase II/III trials
  (> 6 weeks duration: Seroquel; N =260, haloperidol; N=41)
- Uncontrolled Phase II/III trials
  (Seroquel; N=1256)

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).

5.1.2 Plasma glucose data

In the Seroquel NDA, glucose data were collected in 5 trials: 3 short-term placebo-controlled trials (204636/0008, 5077IL/0004, 5077IL/0006), 1 short-term comparator-controlled trial (204636/0007), and 1 long-term comparator-controlled trial (5077IL/0015).

AstraZeneca has been asked by the Agency to provide details on the mean change from baseline in plasma glucose levels, and the number of patients meeting criteria for a markedly abnormal glucose concentration.

5.1.2.1 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 following trial pools:

- Short-term placebo controlled trials
  (Seroquel; N=230, placebo; N=143)
- Short-term comparator controlled trials
  (Seroquel; N=93, chlorpromazine; N=92)

- Long-term comparator controlled trials
  (Seroquel N=170, haloperidol; N=35)

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.

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

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) 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.

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 during of exposure of trial treatment on the number of patient with a markedly high glucose level, the above data will be summarized in 2 trial pools: short-term trials and long-term trials.

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.

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.

5.2 Results

5.2.1 Adverse event data

5.2.1.1 Phase I trials

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

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

COSTART term[a]	Number (%) of patients
	Seroquel (N=300)
Thirst	0
Polyuria	1 (0.3)
Urinary frequency	2 (0.7)
Weight gain[b]	1 (0.3)
Hyperglycemia	1 (0.3)
Diabetes mellitus	0
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**5 (1.7)**
Total number of events	**5**
Total patient year exposure[c]	**8.0**
Incidence density[d]	**0.6**

[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

Only 5 patients (1.7%) had adverse events possibly related to disturbances in glucose metabolism in the Phase I trials. No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. Urinary frequency was the most commonly reported event in these trials.

None of the events in Table 2 were considered serious by the Investigator, or led to withdrawal from treatment.

5.2.1.2 Controlled Phase II/III trials

(a) Short-term trials

The number (%) of patients with adverse events possibly related to 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 related to disturbances in glucose metabolism in the short-term controlled Phase II/III trials

COSTART term[a]	Number (%) of patients			
	Seroquel (N=1450)	Placebo (N=206)	Haloperidol (N=279)	Chlorpromazine (N=100)
Thirst	3 (0.2)	0	0	0
Polyuria	1 (<0.1)	0	0	1 (1.0)
Urinary frequency	2 (0.1)	0	1 (0.4)	0
Weight gain[b]	20 (1.4)	0	3 (1.1)	0
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 patients with events	**24 (1.7)**	**0**	**4 (1.4)**	**1 (1.0)**
Total number of events	**26**	**0**	**4**	**1**
Total patient year exposure[c]	**119.6**	**14.6**	**24.8**	**9.2**
Incidence density[d]	**0.2**	**0**	**0.2**	**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
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Twenty-four patients (1.7 %) treated with Seroquel had adverse events possibly related to 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.

Two patients each had 2 events in the Seroquel group; 1 patient had thirst and weight gain, and 1 patient 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 (20 patients, 1.4%); this occurred at a similar incidence as that in the haloperidol group (1.1%).

Of the 20 patients with weight gain in the Seroquel group, 1 patient was withdrawn from treatment due to the 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 2 weeks), this patient also withdrew for reasons of somnolence and abdominal distension. A full narrative of this patient is presented in Appendix A.

Apart from the 1 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.

(b) Long-term trials

The number (%) of patients with adverse events possibly related to 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 patients with adverse events possibly related to 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]	11 (4.2)	0
Hyperglycemia	0	0
Diabetes mellitus	0	0
Diabetic ketoacidosis	0	0
Hyperosmolar coma	0	0
Total number of patients with events	**12 (4.6)**	**0**
Total number of events	**12**	**0**
Total patient year exposure[c]	**79.3**	**17.6**
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

Twelve patients (4.6%) treated with Seroquel had adverse events possibly related to 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 related to 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.

5.2.1.3 Uncontrolled Phase II/III trials

The number (%) of patients with adverse events possibly related to 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 related to disturbances in glucose metabolism in the uncontrolled Phase II/III trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=1256)
Thirst	1 (0.1)
Polyuria	1 (0.1)
Urinary frequency	3 (0.2)
Weight gain[b]	38 (3.0)
Hyperglycemia	2 (0.2)
Diabetes mellitus	3 (0.2)
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**45 (3.6)**
Total number of events	**48**
Total patient year exposure[c]	**386.2**
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
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

In total, 3.6 % of patients had adverse events possibly associated with disturbances in glucose regulation in the uncontrolled trials.

Three patients each had 2 events: 1 patient had hyperglycemia and urinary frequency, 1 patient had thirst and polyuria and 1 patient had diabetes mellitus and weight gain. Weight gain was the most frequently reported event in these trials.

No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Three cases (0.2%) of diabetes mellitus were reported. Full narratives for each patient are presented in Appendix A. In

2 cases (5077IL/0012/0046/4603 and 5077IL/0015/0005/0509), the patients had a history of diabetes. In the final 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 cases of diabetes mellitus were considered by the Investigator to be related to trial therapy. In addition, none of the 3 cases were considered by the Investigator to be serious, or led to withdrawal of treatment.

Two patients had hyperglycemia in these trials. In both cases, the Investigator considered the events to be serious, and the patients were withdrawn from treatment. Full narratives of both patients are presented in Appendix A. Both patients had significant confounding factors: 1 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. Neither case was considered by the Investigator to be related to treatment with Seroquel.

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

5.2.2 Plasma glucose data

5.2.2.1 Mean change from baseline in random plasma glucose levels

The mean changes from baseline to the end of treatment in plasma glucose levels are presented in Table 6 (placebo-controlled trials), Table 7 (short-term comparator-controlled trials) and Table 8 (long-term comparator-controlled trials).

Table 6 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				
		LSMean	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 squares 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 7 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term comparator-controlled trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	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 squares 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 8 Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	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	0.9333

LS Least squares 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

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).

5.2.2.2 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 postbaseline has been summarized in Table 9 (short-term trials) and Table 10 (long-term trials), according to the baseline glucose level.

Table 9 Number (%) of patients 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 patients 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 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 glucose ≥ 200 mg/dl at any time divided by the total patient year exposure N is based on the number of patients with both baseline and end of treatment glucose data

Table 10 Number (%) of patients 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 patients 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**
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/0006
[b] % uses total number of patients in baseline subgroup as a denominator

[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 glucose ≥ 200 mg/dl at any time divided by the total patient year exposure
N is based on 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).

The proportion of patients 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).

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 analyzed 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, 3 patients received haloperidol, 1 patient received placebo and 16 patients received Seroquel. Narratives of all 20 patients are provided in Appendix A.

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 3 had histories of hyperglycemia or diabetes.

The single placebo patient with post baseline hyperglycemia had a baseline glucose of 142 mg/dl. Four of 6 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:

(a) 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 1 post-baseline glucose value ≥ 200 mg/dl.

In only 5 of the 12 patients was the last glucose value >200mg/dl. In 3 of these 5 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 2 patients, repeated hyperglycemia was not observed since only the last glucose determination was ≥200mg/dl.

Seven of the 12 patients had baseline glucose values <200mg/dl, a last glucose of <200mg/dl and at least 1 post baseline assessment of ≥200mg/dl. In 6 of these 7 patients only 1 of several post-baseline assessments was ≥200mg/dl. In the seventh of these patients 3 of 6 determinations were ≥200mg/dl, but the last glucose value was 149.5 mg/dl, only 7.2mg/dl greater than the baseline value.

None of these 12 patients had a blood glucose determination >300mg/dl.

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.

(b) 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 1 post-baseline glucose value ≥ 200 mg/dl. Two of the 4 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.

5.3 Discussion

5.3.1 Adverse event data

The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies (1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials [≤ 6 weeks duration], 4.6% in the long-term controlled [> 6 weeks duration] and 3.6% in the uncontrolled trials).

After adjusting for time-on-study, the incidence of adverse events possibly related to disturbances in glucose metabolism did not increase as the duration of exposure to Seroquel increased (incidence density of 0.6 for the Phase I trials, 0.2 for the short-term controlled trials, 0.2 for the long-term controlled trials and 0.1 for the uncontrolled trials).

A total of 2419 patients was exposed to Seroquel across the Phase I, short- and long-term controlled Phase II/III, and uncontrolled trials in the Seroquel NDA. No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Diabetes mellitus was reported in just 3 (0.1%) patients (5077IL/0012/0046/4603, 5077IL/0014/0036/3605 and 5077IL/0015/0005/0509, Appendix A). All 3 cases were reported in the uncontrolled trials. Two of the 3 patients had a history of diabetes. The third patient is reported to have 'recovered' from the diabetes following treatment with glibenclamide and continued treatment with Seroquel. None of the 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 (67 of 2419 patients, 2.8%). Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program had diabetes mellitus (5077IL/0015/0005/0509, Appendix A). This patient had diabetes at baseline (for which they were receiving treatment) and subsequently had 'poorly controlled' diabetes recorded as an adverse event. These observations would indicate that weight gain in patients treated with Seroquel is not a risk factor for the development of diabetes. This is not surprising, as our latest analyses have shown that the actual weight gain associated with Seroquel treatment is minimal, even in the long-term (a mean gain of 1.87 kg [median 1.20 kg] over 1.5 years is observed; for further details see Appendix C). It should be noted that AstraZeneca has already alerted the Prescriber to the possibility of weight gain with Seroquel via the inclusion of a statement in the US Prescribing Information.

There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due events possibly related to glucose dysregulation.

Two patients were withdrawn from treatment due to hyperglycemia (in the uncontrolled trials); both events were considered serious by the Investigator. One of these patients (5077IL/0012/0093/9303, Appendix A) was a known diabetic with a history of hyperglycemia before entering the trial, and the other patient (5077IL/0013/0001/0109, Appendix A) had a history of borderline elevated glucose levels. The investigator did not consider either case to be related to treatment with Seroquel. One patient was withdrawn from treatment due to weight gain (in the short-term controlled trials). Somnolence and abdominal distension were also documented as reasons for withdrawal in this patient. The event was not considered serious by the Investigator.

Apart from the 2 cases of hyperglycemia, none of the other events possibly related to disturbances in glucose regulation in the clinical trial program were considered serious by the Investigator.

5.3.2 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).

A detailed review of the patients with a glucose value ≥ 200 mg/dl revealed that the majority of elevations were sporadic (ie not consistently observed during treatment) and did not exceed 300 mg/dl at any time. Further, *none* of the patients had symptoms of diabetes. It is likely that the values observed reflect variations in a parameter that is strongly influenced by the interval since that last meal, glucose content of the last meal, state of hydration, and many other factors.

5.4 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, there was no evidence from the clinical data of a direct link between weight gain in patients treated with Seroquel and the onset of diabetes.

6 REVIEW OF POSTMARKETING DATA

In response to Part 3 of the FDA's request, spontaneous postmarketing reports received by AstraZeneca since Seroquel's US approval (September 1997) up to May 2000 have been thoroughly reviewed for possible cases of hyperosmolar coma, new-onset diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain.

6.1 Results

6.1.1 Hyperosmolar coma

There have been no postmarketing reports of hyperosmolar coma.

6.1.2 New-onset diabetes mellitus

There have been 12 spontaneous postmarketing reports of new-onset diabetes mellitus (including 2 literature reports). Narratives of all 12 patients are presented in Appendix B.

The age range for patients with new onset diabetes mellitus is 12 to 48 years, with an average age at onset of 32.5 years (median = 34 years). There is a male predominance, with males constituting 75% of all reports. Daily Seroquel dosages ranged from 50 mg to 750 mg, with an average daily dose of 385 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 4.9 months with a range of 15 days to 21 months (median = 2.0 months). Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl (median 474= mg/dl).

Weight gain was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 1999UW03532).

Weight loss was reported in 1 of the 12 patients with new-onset diabetes (2000UW01164).

Diabetic ketoacidosis was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 2000UW01164).

Dose-related loss of glycemic control was reported in 2 of the 12 patients with new-onset diabetes mellitus (1999UW00969 and 1998UW48512).

One patient developed Type 1 diabetes mellitus (2000UW00266).

In addition to the 12 patients with new-onset diabetes described above, AstraZeneca has received 4 reports describing exacerbation of pre-existing diabetes mellitus.

6.1.3 Diabetic ketoacidosis

There have been 3 postmarketing spontaneous reports of diabetic ketoacidosis. Narratives of all 3 patients are presented in Appendix B.

The age range is 25 to 58 with an average age at onset of 42 years (median= 43 years). All 3 patients were male. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 583 mg (median = 750 mg). The average time interval between initial therapy and the date of the reported event was 11.0 months with a range of 1 to 21 months (median =11 months). Blood glucose concentrations at clinical presentation for these patients were not provided.

Two of the 3 patients with diabetic ketoacidosis also developed new-onset diabetes mellitus. (1999AP05757 and 2000UW01164). The former patient gained an unspecified amount of weight and the latter patient lost 13.6 kg.

Another patient (1998UW49554) with a pre-existing diabetic condition died due to complications of diabetes mellitus.

6.1.4 Hyperglycemia

There have been 2 postmarketing spontaneous reports of hyperglycemia. Narratives of both patients are presented in Appendix B.

Blood glucose concentrations were not provided for either patient. One report (2000UW01047) involved a 47-year-old female who developed weight gain and hyperglycemia after taking Seroquel 150 mg daily for 30 months. The other report (1998AP50408) contains scant information, except the daily Seroquel dose which was 750 mg.

6.1.5 Weight gain

There have been 38 spontaneous postmarketing reports and 4 literature reports of weight gain associated with Seroquel therapy.

Patients ranged in age from 8 to 70 years of age with a mean of 38 years (median = 36 years). There is a slight female predominance with females constituting 55% of reports in which gender was specified. Reported weight gain ranged from 0.9 kg to 31.8 kg with the average reported weight gain being 12.5 kg (median = 10.7 kg). The average time interval between initial therapy and the date of the reported event was 6.8 months with a range of 10 days (2.2 kg) to 2 years (18.1 kg) and a median of 4 months.

Diabetes mellitus was reported in 2 of the 38 patients with weight gain (1999AP05757 and 1999UW03532).

6.2 Discussion

Since the approval of Seroquel in the US in September 1997, it is estimated that over 623,000 patients have been exposed to Seroquel (see Section 7). Despite this extensive exposure, only a small number of cases of diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain have been reported.

Many of the cases reported had confounding factors. Six of the 12 patients with new-onset diabetes were reported as using concomitant medications known to be associated with glucose dysregulation and diabetes mellitus, including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, and 1999UW00969). Few, if any, of the 12 patients had baseline fasting glucose levels.

One of the 3 patients with diabetic ketoacidosis (2000UW01164) is reported to have used concomitant medications known to impair glucose tolerance and cause diabetes mellitus (venlafaxine). Another patient (1998UW49554) had a pre-existing diabetic condition.

In the patients with weight gain, there are several confounding factors to note. Two patients (1999UW01496 and 1998UW46392) developed edema and 1 patient (1999AP00761) was diagnosed with congestive heart failure. Edema and heart failure are both labeled adverse events that are known to contribute to weight gain secondary to fluid retention and accumulation. There was 1 report (1999UW02120) describing a negative dechallenge in which the accrued weight remained despite discontinuation of Seroquel treatment. Two patients (1999UW02120 and 1998UW48690) had concomitant hypothyroidism, a known cause for weight gain. In addition, 1 patient (1999AP05242) developed hypothyroidism after starting Seroquel treatment.

Unfortunately, several postmarketing reports contained only scant information that precluded further detailed analysis of these cases.

The current US Seroquel package insert is labeled for diabetes mellitus, hyperglycemia, and weight gain as Adverse Reactions. Details are provided below.

Under the category of Other Adverse Events Observed During the Pre-marketing Evaluation of SEROQUEL in the insert, diabetes and hyperglycemia are listed as an infrequent experience (events occurring in 1/100 to 1/1000 patients). Weight gain (2%) is included as a treatment-emergent adverse experience in 3- to 6-week placebo-controlled clinical trials. The package insert also alerts the Prescriber to a statistically significantly greater incidence of weight gain (≥ 7% of body weight) for SEROQUEL (23%) compared to placebo (8%). In addition, reference is made

to spontaneously elicited adverse event data from a study comparing five fixed doses of Seroquel (75 mg, 150 mg, 300 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. The insert states that logistic regression analysis revealed a positive dose response ($p < 0.05$) for weight gain in this analysis.

The package insert does not contain any details of diabetic ketoacidosis or hyperosmolar coma. However, only 3 spontaneous reports of diabetic ketoacidosis have been received to date in patients using Seroquel (indicating that there does not appear to be a signal that Seroquel is associated with diabetic ketoacidosis) and there have been no reported cases of hyperosmolar coma.

AstraZeneca has paid particular attention to the incidence of patients with both weight gain and diabetes. Only 2 patients were reported to have had concomitant weight gain and diabetes mellitus. Thus there does not appear to be a link between these 2 conditions.

6.3 Conclusion

It is concluded that that the current Seroquel package label accurately describes patient experiences to date of diabetes mellitus (and related complications), hyperglycemia, and weight gain.

7 PATIENT EXPOSURE ESTIMATION

In response to Part 4 of the FDA's request, AstraZeneca has calculated the extent of exposure to Seroquel across the clinical trial program, and estimated the extent of exposure to Seroquel from postmarketing experience.

7.1 Clinical trials

7.1.1 Phase I trials

A total of 300 patients were exposed to Seroquel in the Phase I trials.

The mean daily dose and duration of Seroquel use in the Phase I clinical trials are presented in Table 11.

Table 11 Mean daily dose and duration of exposure to Seroquel in the Phase I trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	33	0	0	0	0	0	33 (11)
2 to 7	83	5	10	1	0	0	99 (33)
8 to 14	1	3	19	18	29	0	70 (23)
15-21	0	0	21	46	9	7	83 (28)
22-35	0	8	1	5	1	0	15 (5)
Total (%)	117 (39)	16 (5)	51 (17)	70 (23)	39 (13)	7 (2)	300 (100)

Approximately 40% of subjects received Seroquel for less than 7 days. A total of 55% of subjects had mean doses of Seroquel within the clinically effective dose range (>150 to < 800 mg/day). Fifteen percent of subjects had mean daily doses that were greater than 450 mg/day.

7.1.2 Controlled Phase II/III trials

A total of 1710 patients were exposed to Seroquel in the controlled Phase II/III trials.

The mean daily dose and duration of Seroquel use in the controlled Phase II/III clinical trials are presented in Table 12.

Table 12 Mean daily dose and duration of exposure to Seroquel in the controlled Phase II/III trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	14	0	0	0	1	0	15 (1)
2 to 7	59	24	60	4	1	0	148 (9)
8 to 14	63	17	60	79	21	2	242 (14)
15 to 21	36	22	37	55	19	2	171 (10)
22 to 28	23	6	23	40	19	1	112 (7)
29 to 35	17	2	16	24	9	8	76 (4)
36 to 42	97	26	94	285	138	63	703 (41)
43 to 112	39	6	29	51	27	9	161 (9)
113 to 183	5	0	7	0	9	0	21 (1)
184 to 365	16	4	15	0	20	0	55 (3)
366 to 548	0	0	2	0	3	1	6 (0)
Total (%)	369 (22)	107 (6)	343 (20)	538 (32)	267 (16)	86 (5)	1710 (100)

Most subjects (86%) received Seroquel for 6 weeks or less because most exposure in the controlled trials occurred in short-term trials. The majority of subjects (72%) had mean daily doses of Seroquel that were greater than 150 mg/day; 21% had mean daily doses that were greater than 450 mg/day.

7.1.3 Uncontrolled Phase II/III trials

A total of 1256 patients were exposed to Seroquel in the uncontrolled trials. Of these, 847 patients had taken part in the controlled trial program.

The mean daily dose and duration of Seroquel use in the uncontrolled Phase I/III clinical trials are presented in Table 13.

Table 13 Mean daily dose and duration of exposure to Seroquel in the uncontrolled trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	6	1	1	0	0	0	8(1)
2 to 7	17	18	31	11	2	1	80(6)
8 to 14	7	4	27	19	22	7	86 (7)
15 to 21	7	2	10	30	25	15	89 (7)
22 to 28	8	5	25	40	28	18	124 (10)
29 to 35	2	2	5	15	29	13	66 (5)
36 to 42	3	6	10	10	14	14	57 (5)
43 to 112	10	12	36	57	80	82	277 (22)
113 to 183	1	2	24	49	65	46	187 (15)
184 to 365	1	5	41	58	60	62	227 (18)
366 to 548	0	1	8	10	16	17	52 (4)
549 to 730	0	0	1	0	0	1	2 (0)
730	0	0	0	0	0	1	1 (0)
Total (%)	62 (5)	58 (5)	219 (17)	299 (24)	341 (27)	277 (22)	1256 (100)

A total of 59% of subjects had been given Seroquel for longer than 6 weeks: 282 subjects were exposed to Seroquel for 6 months or longer, 55 subjects were exposed for more than 1 year and 1 subject was exposed to Seroquel for more than 2 years. Most subjects (90%) had mean daily doses of Seroquel that were greater than 150 mg/day, whereas 49% of subjects had mean daily doses greater than 450 mg/day.

7.2 Postmarketing experience

It is difficult to obtain a precise estimate of the number of patients that have been exposed to Seroquel since launch. However, a recent audit of the NDC database indicated that, on average, a patient received 3.84 prescriptions for Seroquel. In post-launch period to 30 June 2000, 2,393,000 prescriptions have been written for Seroquel in the US. This would suggest that approximately 623,000 unique patients have been exposed to Seroquel since launch, representing approximately 199,000 patient years (assuming that each prescription covers a 1- month period).

8 CORRESPONDENCE WITH REGULATORY AGENCIES

In response to Part 5 of the FDA's request, AstraZeneca has reviewed all correspondence with regulatory agencies regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

8.1 Results

There have been no issues raised verbally or formally in correspondence with foreign regulatory agencies related to the events of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, and hyperglycemia associated with Seroquel.

Questions relating to weight gain during the clinical program were asked by the French and Swiss agencies during their national reviews and also by Spain during the question and answer period in the European Mutual Recognition (MR) procedure conducted in the latter half of 1999.

In preclinical assessment, the Swedish Medical Products Agency (MPA) and the Japanese Ministry of Health and Welfare (MHW) asked the same question during their national reviews regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study. This topic is also addressed in Part 1 of this FDA response.

Copies of all the questions and company responses are provided in Appendix D.

8.2 Discussion

In terms of weight gain, it should be noted that the company has already taken the step globally of alerting the Prescriber to the possibility of limited weight gain with Seroquel via the inclusion of a statement in Section 4.9 (possible adverse reactions) of the Core Data Sheet for the product.

In the spirit of this, the Adverse Reactions section of the US Professional Information Brochure advises the physician that there is a statistically significantly greater incidence of weight gain for Seroquel (23%) compared to placebo (6%).

The explanation given to both MPA and MHW regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study was accepted by both agencies.

9 POTENTIAL COLLABORATION WITH OTHER DATABASES

We are investigating the possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

References

Cavaziel Fet al (1981) Studi sul controllo dopaminergico della secrezione insulinica nell'uomo. J Endocrinol Invest Supp 1 309-311

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183–1197

Landgraf R et al (1977) Prolactin: a diabetic hormone. Diabetologia 13 99-104

Markoff E et al (1990) Effects of prolactin and glycosylated prolactin on insulin synthesis and insulin release from cultured rat pancreatic islets. Pancreas 5 99-103

Michaels RL et al (1987) Prolactin enhances cell-to-cell communication among B-cells in pancreatic islets. Diabetes 36 1098-1103

Morricone L et al (1990) Effect of acute administration of metoclopramide on insulin secretion in man. Acta Diabetol Lat 27 53-57

Nielsen JH et al (1982) Effects of growth hormone, prolactin and placental lactogen on insulin content and release, and deoxyribonucleic acid synthesis in cultured pancreatic islets. Endocrinology 110 600-606

Unger RH et al (1981) Glucagon physiology, pathophysiology and morphology of the pancreatic A-cells. Elsevier Amsterdam

Woodman DD (1997) Laboratory animal endocrinology. John Wiley and Sons Ltd

APPENDIX A

Patient narratives: clinical data

Patients withdrawn from treatment due to adverse events possibly associated with disturbances in glucose metabolism

5077IL/0012/ 0007/0708 Seroquel

Abdomen enlarged, Weight gain, Somnolence

This 37-year old, white woman with chronic paranoid schizophrenia was withdrawn on Day 10 for abdominal distension, abnormal weight gain, and drowsiness while receiving Seroquel 450 mg/day, administered on a twice-daily basis. The drowsiness resolved 1 day later. Her weight gain was 2.0 kg over 2 weeks, and returned to pretrial levels 6 days after withdrawal, as did the abdominal distension. She was receiving no concurrent medication at entry and had an unremarkable medical history other than tubal ligation. The abdominal distension, abnormal weight gain, and drowsiness were considered by the investigator to be probably related to Seroquel.

5077IL/0012/ 0093/9304 Seroquel

Hyperglycemia

This 53-year-old, white woman with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 34 (Seroquel 200 mg/day) due to hyperglycemia (glucose value not available). The subject was a known diabetic and had hyperglycemia noted prior to entry into the trial. Other significant medical history included hypertonia and angina. Concurrent medications included ascorbic acid/ferrous sulfate combination, insulin protamine injection/insulin regular combination, glycerol trinitrate, fenofibrate, REDACTED, insulin protamine injection, insulin regular, and drotaverine. On Day 18 (Seroquel 200 mg/day), hyperglycemia (COSTART term hyperglycemia) was reported as an adverse event (glucose value not available). The hyperglycemia resolved 3 weeks (Day 55) after withdrawal from trial treatment. The event was considered by the investigator to be moderate in intensity and probably not related to trial treatment.

5077IL/0013/ 0001/0109 Seroquel

Hyperglycemia

This 44-year-old, black man with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 10 (Seroquel 150 mg/day) due to hyperglycemia. Medical history was significant for borderline elevated glucose levels (untreated), Bell's palsy, back pain, gynecomastia, peptic ulcer disease, hiatal hernia, obesity, abdominal discomfort, and urinary hesitancy. Concurrent medications included ranitidine, pseudophedrine/triprolidine combination, and glipizide. On Day 8, the fasting blood glucose level previously drawn was discovered to be 392.72 mg/dl (normal range 68 to 115 mg/dl). A repeat level drawn on Day 8 was 407.1 mg/dl. The subject was sent to the emergency room for a medical consult, where he was started on glipizide and placed on a special diet prior to his return to the unit that same day. On Day 10 (Seroquel 600 mg), he complained of nausea, dizziness, and blurred vision, and vomited his lunch. A blood glucose level was immediately drawn with a result of 1104.3 mg/dl. The subject was again transferred to the emergency room and was admitted to the medical intensive care unit of the hospital, where he was started on intravenous insulin and hydration. At this time, trial treatment was discontinued. By Day 11, his blood glucose had decreased to the 198.1 mg/dl range and the subject had otherwise returned to his baseline health. The insulin drip was discontinued on Day 12 and he was maintained on subcutaneous insulin until Day 15, when this was switched to glyburide and he was transferred back to his original unit. Glucose remained stable in the 198.1 mg/dl range. The subject did not receive any further trial treatment after Day 10 due to difficulties in following the subject at another hospital. The investigator considered restarting the subject on the trial treatment once he returned to his original unit; however, at the request of the subject's spouse, this was not done. The investigator considered the hyperglycemia to be severe in intensity and not related to trial treatment.

Patients with adverse events of diabetes mellitus

5077IL/0012/0046/4603 Seroquel (controlled trials), Seroquel (open label extension)

This patient is a 35-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day. The patient had a history of eye esotropia and diabetes mellitus. The patient was receiving daonil for diabetes before the start of the trial. During the trial adverse events of weakness, sleepiness and constipation were all reported as mild and possibly related. The patient discontinued Seroquel therapy at a dose of 450 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of headache, insomnia and unstable diabetes were reported. The unstable diabetes was reported 9 days into open label treatment. The patient was receiving 300 mg/day Seroquel. The event was considered 'moderate' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed insulin and glucophage for the diabetes.

5077Il/0014/0036/3605 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 51-year old white female presenting with paranoid schizophrenia who began haloperidol at a dose of 1mg/day. The patient had a past history of hypertension.

During the trial the adverse event of moderate hypertension, related to therapy, was recorded. The patient discontinued haloperidol therapy at a dose of 10 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of diabetes mellitus and infection were reported. The diabetes mellitus was reported 61 days into open label treatment. The patient was receiving 400 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide for the diabetes.

5077IL/0015/0005/0509 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 40-year old black female presenting with paranoid schizophrenia who began haloperidol at a dose of 2 mg/day. She had a medical history of otitis media, tooth infections, chronic headaches, EPS (benzatropine), cardiomegally (mild hypertension), bronchitis, urinary tract infection (salpingeltomy), diabetes, depression (nortriptyline), anxiety (lorazepam), insomnia (chloral hydrate). The patient was prescribed glibenclamide for the diabetes before the trial.

During the trial adverse events of hand tremors, muscle stiffness and cogwheel rigidity were all reported as moderate and probably related were reported. The patient discontinued haloperidol therapy at a dose of 12 mg/day on Day 28. The reason for discontinuation was reported as adverse reaction/intercurrent illness.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of tongue tremors, constipation, weight gain, tooth abscess, septicemia, insomnia and poorly controlled diabetes mellitus were reported. The diabetes mellitus was reported 344 days into open label treatment. The patient was receiving 500 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide and received insulin injections for the diabetes.

Patients with plasma glucose ≥ 200 mg/dl at any time

204636/0007/0003/0002 Seroquel

This patient is a 35-year old white female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 50mg/day on 16-May-1991(Day 0). She had a medical history of anemia (ferrous sulfate, folic acid), psychosis (lithium carbonate, stelazine) and depression (lofepramine). Pre-trial antipsychotic medication was not recorded. She received EPS medications -unspecified (agitation), benzodiazepines (agitation) and chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 1000mg/day by Day 19. The patient's weight was 63.0kg on Day 0 and 66.0kg on Day 27.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
15-May-91 (1)	162
23-May-91 (7)	133.3
30-May-91 (14)	221.6
05-Jun-91 (20)	97.3
12-Jun-91 (27)	86.5

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'treatment failure'.

204636/0008/0001/0021 Seroquel

This patient is a 21-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 05-Aug-1991(Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 76.2kg on Day 0 and 76.2kg on Day 10.

During treatment adverse events of drowsiness, depressed thyroid stimulation, thyroxine and triiodothyronine were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
26-July-91 (-10)	178.3
12-Aug-91 (7)	207.2

The patient discontinued Seroquel therapy at a dose of 50 mg/day on Day 10. The reason for discontinuation was reported as 'refused to continue'.

204636/0008/0005/0003 Seroquel

This patient is a 55-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-Sept-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 6. The patient's weight was 81.0kg on Day 0 and 82.0kg on Day 41.

During treatment an adverse event of severe agitation which was possibly related was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
29-Aug-91 (-4)	167.5
17-Sept-91 (15)	210.8
23-Sept-91 (21)	196.4
01-Oct-91 (29)	129.7
09-Oct-91 (37)	106.3
14-Oct-91 (42)	90.1

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0009/0002 Seroquel

This patient is a 59-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day on 20-Aug-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded.

During the trial the patient was dosed Seroquel up to a level of 350mg/day by Day 13. The patient's weight was 88.9kg on Day 0 and 91.6kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Aug-91 (-6)	142.3
27-Aug-91 (7)	230.6
02-Sept-91 (13)	221.6
09-Sept-91 (20)	129.7
16-Sept-91 (27)	252.2
23-Sept-91 (34)	136.9
30-Sept-91 (41)	149.5

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0020/0005 Seroquel

This patient is a 44-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 25-July-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 5. The patient's weight was 75.2kg on Day 0 and 77.5kg on Day 27.

During treatment adverse events of probably related moderate headache and possibly related moderate agitation were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
24-July-92 (-1)	234.2
31-July-92 (6)	257.6

07-Aug-92 (13)	322.5
13-Aug-92 (19)	264.8
20-Aug-92 (26)	226.9
24-Aug-92 (30)	-

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'refused to continue'

204636/0008/0026/0001 Seroquel

This patient is a 38-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 13-May-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 500mg/day by Day 9. The patient's weight was 79.0kg on Day 0 and 78.0kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
30-Apr-92 (-13)	118.9
20-May-92 (7)	100.9
09-Jun-92 (27)	198.2
16-Jun-92 (34)	205.3
23-Jun-92 (41)	172.9

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0026/0006 Placebo

This patient is a 41-year old white female presenting with paranoid schizophrenia who began the trial on 14-July-1992 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel placebo. The patient's weight was 110.0kg on Day 0 and 115.0kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Jul-92 (0)	142.3
21-Jul-92 (7)	167.5
28-Jul-92 (14)	223.4
04-Aug-92 (21)	120.7
11-Aug-92 (28)	207.2
18-Aug-92 (35)	219.8
25-Aug-92 (42)	223.4

The patient discontinued on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0028/0110 Seroquel

This patient is a 36-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 08-Nov-1991 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 75.5kg on Day 0 and 74.6kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Nov-91 (-4)	160
14-Nov-91 (6)	154
22-Nov-91 (14)	137
29-Nov-91 (21)	131
06-Dec-91 (28)	218

13-Dec-91 (35)	158
20-Dec-91 (42)	148

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0031/0403 Seroquel

This patient is a 36-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 10-Mar-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received chloral hydrate (sleep) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 11. The patient's weight was 76.8kg on Day 0 and 77.3kg on Day 22.

During treatment an adverse event of possibly related mild dizziness was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
06-Mar-92 (-4)	103
17-Mar-92 (7)	155
24-Mar-92 (14)	190
01-Apr-92 (22)	228

The patient discontinued Seroquel therapy at a dose of 550mg/day on Day 22. The reason for discontinuation was reported as 'lack of efficacy'.

5077IL/0004/0001/0008 Seroquel

This patient is a 40-year old black male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 09-Jan-1990 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 200mg/day by Day 12. The patient's weight was 83.6kg on Day 0 and 90.9kg on Day 20.

During treatment adverse events of elevated SGPT, sedation, headache and tachycardia were reported, these were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Jan-90 (-5)	74
09-Jan-90 (0)	106.3
13-Jan-90 (4)	259.4
17-Jan-90 (8)	122.5
21-Jan-90 (12)	104.5
25-Jan-90 (16)	113.5
29-Jan-90 (20)	111.7

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 20. The reason for discontinuation was reported as 'completed study'.

5077IL/0006/0001/0114 Seroquel

This patient is a 58-year old black male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 07-Jan-1992 (Day 0). He had a pre-trial medical history of eczema, fungal infection, hypertension, hepatomegaly, scrotal mass, perianal fissures, dementia, cataracts, schizophrenia, bipolar disorder and tardive dyskinesia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 27. The patient's weight was 61.4kg on Day 0 and 61.4kg on Day 34 and his height was recorded as 175 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
03-Jan-92 (-4)	97
13-Jan-92 (6)	95
20-Jan-92 (13)	115

27-Jan-92 (20)	73
03-Feb-92 (27)	62
10-Feb-92 (34)	215

The patient discontinued Seroquel therapy at a dose of 750mg/day on Day 34. The reason for discontinuation was not recorded.

5077IL/0006/0011/1110 Seroquel

This patient is a 48-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 19-Mar-1992 (Day 0). He had a pre-trial medical history of tardive dyskinesia and schizophrenia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation, insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 600mg/day by Day 29. The patient's weight was 82.5kg on Day 0 and 86.8kg on Day 41 and his height was recorded as 173 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Mar-92 (-2)	133
25-Mar-92 (6)	157
01-Apr-92 (13)	186
08-Apr-92 (20)	193
15-Apr-92 (27)	210
22-Apr-92 (34)	164
29-Apr-92 (41)	158

The patient discontinued Seroquel therapy at a dose of 400mg/day on Day 41. The reason for discontinuation was reported as 'completed study'

5077IL/0015/0012/1205 Haloperidol

This patient is a 34-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 18-Feb-1994 (Day 0). He had a pre-trial medical history of bronchitis, hyperglycemia, and alcohol and drug abuse. Pre-trial the patient received haloperidol for schizophrenia, this was stopped on 17-Feb-1994 (Day -1). He received the following concomitant medication during the trial: cogentin (EPS prophylaxsis), diabeta (hyperglycemia), hydrocodone, iodine, aspirin (left foot pain, body aches), prozac (unknown), contac (nasal congestion), 4-way nasal spray (nasal congestion), sinutab (sinus headaches), orudis (groin pain), flexeril, voltaren (left sciatic pain) and erythromycin (sore throat). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 6. The patient's weight was 136.4kg on Day 0 and 130.5kg on Day 357 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the study were as follows:

Date (day)	Glucose mg/dl
17-Feb-94 (-1)	268
04-Aug-94 (167)	516
16-Feb-95 (357)	328

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0013/1309 Seroquel

This patient is a 43-year old hispanic female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 18-May-1994 (Day 0). She had a pre-trial medical history of head injury, anemia, hepatitis, hypothyroidism, substance abuse and pollen allergies. Pre-trial the patient received trifluoperazine for schizophrenia, this was stopped on 17-May-1994 (Day -1). She received the following concomitant medication during the trial: propanolol (akathisia , anxiety), cogentin (EPS), triphosil-28 (oral contraceptive), chloral hydrate (anxiety), lorazepam (agitation), chlortrimetan (sinus congestion), flu shot (flu prevention), ibuprofen and tylenol (intermittent back/neck pain) During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 106.4kg on Day 0 and 99.1kg on Day 358 and her height was recorded as 168 cm.

During treatment an adverse event of increased sedation was reported, this was reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-May-94 (-9)	254
31-Oct-94 (166)	250
14-May-95 (358)	122

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 358. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0019/1903 Seroquel

This patient is a 46-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 23-Nov-1993 (Day 0). She had a pre-trial medical history of headaches, non insulin dependent diabetes and obesity. Pre-trial the patient received tiotixene for schizophrenia, this was stopped on 22-Nov-1993 (Day -1). She received the following concomitant medication during the trial: diabeta (non insulin dependent diabetes), lorazepam (agitation), lorcet plus, tylenol (headaches), tavist-D (nasal congestion), cataflam, oruvail and flexeril (back pain). The patient was dosed Seroquel at a level of 75mg/day throughout the trial. The patient's weight was 109.5kg on Day 0 and 109.5kg on Day 357 and her height was recorded as 168 cm.

During treatment adverse events of intermittent insomnia and constipation were reported, these were reported as mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-Nov-93 (-12)	245
10-May-94 (168)	313
15-Nov-94 (357)	434

The patient discontinued Seroquel therapy at a dose of 75mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0021/2105 Haloperidol

This patient is a 63 year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 21-Dec-1993 (Day 0). He had a pre-trial medical history of

rash, hypertension, benign prostatic hypertrophy, shortness of breath and untreated elevated blood sugar. Pre-trial the patient received perphenazine for psychosis, this was stopped on 20-Dec-1993 (Day -1). He received the following concomitant medication during the trial: benadryl, chloral hydrate (insomnia) and lorazepam (agitation). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 9. The patient's weight was 109.1kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment an adverse event of probably related mild sedation was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
13-Dec-93 (-8)	327
03-Jan-94 (13)	282

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 15. The reason for discontinuation was reported as 'refused to continue'

5077IL/0015/0023/2310 Seroquel

This patient is a 43-year old male of 'other' ethnic origin presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-July-1994 (Day 0). He had a pre-trial medical history of sinus bradycardia, mild peptic ulcer and stable insulin dependent diabetes. Pre-trial the patient received chlorpromazine for psychosis, this was stopped on 24-Jun-1994 (Day -8). He received insulin NPH (diabetes) during the trial. During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 58.6kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Jun-94 (-15)	363
30-Aug-94 (59)	406

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 59. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0026/2607 Seroquel

This patient is a 52-year old asian male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 15-Dec-1993 (Day 0). He had a pre-trial medical history of myocardial infarction and increased cholesterol. Pre-trial the patient received perphenazine for psychosis, this was stopped on 14-Dec-1993 (Day -1). He received the following concomitant medication during the trial: lorazepam (agitation), lithobid (adjunct Tx schizophrenia), temazepam, chloral hydrate (insomnia), aspirin (heart condition) and mevacor (hypercholesterolemia). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 8. The patient's weight was 79.5kg on Day 0 and 79.3kg on Day 12 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Dec-93 (-1)	192
28-Dec-93 (13)	240

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 12. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0034/3411 Seroquel

This patient is a 41-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 14-Oct-1994 (Day 0). She had a pre-trial medical history of tubal ligation, substance abuse and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Oct-1994 (Day -1). She received the following concomitant medication during the trial: benzatropine (EPS prophylaxsis), desipramine (depression) and micronase (diabetes). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 6. The patient's weight was 101.4kg on Day 0 and 122.7kg on Day 209 and her height was recorded as 168 cm.

During treatment an adverse event of mild dizziness was reported, this was mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl

05-Oct-94 (-9)	186
21-Apr-95 (168)	259

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 209. The reason for discontinuation was reported as 'completed study'.

5077IL/0015/0035/3502 Haloperidol

This patient is a 43-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 14-Mar-1994 (Day 0). He had a pre-trial medical history of depressed hypertension, elevated liver enzymes and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Mar-1994 (Day -1) . He received the following concomitant medication during the trial: lorazepam (agitation), lithium, nortriptyline (depression), glucotrol (diabetes), accupril (hypertension), ativan (increased anxiety), vantin (URI), tylenol, motrin (headache), chloral hydrate (insomnia), alcaine, cyclogyl, mydfrin, profenal, BSS, dexamethasone, garamycin and viscoat (cataract surgery). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 5. The patient's weight was 108.2kg on Day 0 and 106.8kg on Day 364 and his height was recorded as 168 cm.

During treatment an adverse event of serious cataract surgery, unrelated to trial therapy, was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
08-Mar-94 (-6)	191
30-Aug-94 (169)	364
13-Mar-95 (364)	209

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 364. The reason for discontinuation was reported as 'completed protocol'.

APPENDIX B

Patient narratives: postmarketing data

Cases of new-onset diabetes mellitus

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose levels

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 13.6 kg. Fasting blood sugar showed glucose level over 700 mg/dl. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

2000UW00266 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 12-year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170 mg/dl. Concomitant medications include Zoloft, Klonopin, Haldol and depakote.

Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

1999UW03532 Seroquel

Diabetes mellitus, weight gain

A report has been received from a physician concerning a 45-year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes.

Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

1999UW03387 Seroquel

Type II diabetes, drowsiness

A report has been received from a physician concerning a 17-year old Hispanic male patient who had been receiving Seroquel 100 mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

1999UW00969 Seroquel

Complications of diabetes mellitus

A report has been received from a physician concerning a 28-year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240 mg/dl, potassium low, CPK normal, lithium level was not elevated (0.4 or 0.6 mEq/L). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on REDACTED The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending. Follow-up has been requested.

*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no dolls eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli.

Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. 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 the onset. He died on REDACTED The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 4.5 to 7.3 kg weight loss with flu-like symptoms, and blood glucose of 123.8 mg/dl on admission.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 months after starting Seroquel fumarate, the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

1999AP05218 Seroquel

Diabetes during pregnancy

No further information available.

1999AP02989 Seroquel

Diabetes mellitus

This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 308 mg/dl.

1998UW48512 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 98, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycemia. Four months prior to admission blood glucose was 126 mg/dl and 107 mg/dl. At admission blood glucose was 607 mg/dl. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

This patient's details have been published in a literature case report (Sobel, Jaggers and Franz, 1999).

1999AP01985 Seroquel

Non-insulin dependent diabetes

Terse Narrative: Concomitant medication includes cyproterone acetate which can influence carbohydrate metabolism.

1998UW48844 Seroquel

Hyperglycemia, diabetes

A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for 4 weeks and is experiencing hyperglycemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl. Follow-up will be requested.

1999UW00967 Seroquel

Diabetes

A report has been received from a physician concerning a 17-year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Cases of diabetic ketoacidosis

1998UW49554 Seroquel

Cerebrovascular accident, diabetic acidosis, transient ischemic attack, collapse

A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack 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 to cerebrovascular accident. Additional information will be requested.

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose level

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 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 (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

Cases of hyperglycemia

2000UW01047 Seroquel

Cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, excitable, difficulty in waking, negative mood, decreased sex drive, inability to have orgasms

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

1998AP50408 Seroquel

Hyperglycemia (non-serious)

Pharmacist considers hyperglycemia unrelated to Seroquel, however patient's nurse considers the event related.

APPENDIX C

The effect of Seroquel on weight gain

Source material

The weight information provided below has been taken from the interim assessment of Seroquel Trial 5077IL/0051 (an open label extension [OLE] trial; data cut-off date March 28 2000).

Trial 5077IL/0051 is an international, multicentre, open-label extension of treatment with Seroquel for schizophrenic patients who have participated in the Seroquel Phase IIIb clinical trial program (namely Trials 0050, 0052, 0053 and 0054).

Open treatment with Seroquel began, in most cases, with an initial dose-titration period during which the dose was increased according to the patient's clinical condition. Thereafter, Seroquel dosing was flexible, up to a maximum of 800 mg/day, administered twice daily.

Weight data for the analyses are taken from patients who were exposed to Seroquel either during randomized treatment in the feeder trial or open-label Seroquel treatment during OLE.

Analyses

To observe the effect of Seroquel monotherapy on weight gain, the following analyses were undertaken:

- **The effect of Seroquel monotherapy on weight over time (between 1 and 1.5 years)**
  - in patients with weight data *both* at baseline and at 1 specific timepoint during treatment with Seroquel monotherapy: Weeks 53-78

  If a patient had more than 1 visit within each timepoint, then the mean value was taken.

- **The effect of Seroquel monotherapy on weight across the dose range**
  - in patients with weight data at baseline and endpoint

  Data were classified into the following 3 dose ranges (according to the patient's dose of Seroquel at endpoint): ≤ 300 mg, > 300 mg to ≤ 500 mg, > 500 mg. (It should be noted that time on treatment for each patient in this cohort will vary).

Results

In patients with weight data both at baseline and at 1 specific timepoint during Seroquel monotherapy treatment (between 1 and 1.5 years), the mean weight change was 1.87 kg and the median weight change was 1.20 kg (Tables C1 and C2).

Weight change observed at the end of treatment with Seroquel monotherapy was consistent across the dose range (Tables C3 and C4).

Table C1 Patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel	
	Weeks 1-4 (n=130)	Weeks 53-78 (n=130)
Mean weight (kg)	72.57	74.44
Median weight (kg)	70.25	72.00
SD	15.50	15.59
Min	43.0	45.6
Max	128.7	136.0

Table C2 Change from first dose of Seroquel in patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel
	Weeks 53-78 (n=130)
Mean weight change (kg)	1.87
Median weight change (kg)	1.20
SD	7.63
Min	-27.2
Max	25.5

Table C3 Patient absolute weight at baseline and endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Baseline				
Mean weight (kg)	75.88	73.91	73.10	74.37
Median weight (kg)	73.40	71.75	69.70	71.50
SD	16.13	17.08	15.10	14.83
Min	47.5	43.0	50.2	46.2
Max	128.0	146.0	130.0	126.0
Endpoint				
Mean weight (kg)	77.10	74.66	73.30	74.04
Median weight (kg)	75.00	72.00	72.50	72.00
SD	15.69	19.30	16.52	15.52
Min	45.0	46.0	45.8	43.9
Max	128.5	172.8	140.0	135.0

Table C4 Change in weight from baseline to endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Mean weight change (kg)	1.21	0.75	0.20	-0.34
Median weight change (kg)	1.00	-0.25	-0.60	0.00
SD	7.33	7.25	7.86	7.91
Min	-21.8	-14.5	-21.4	-27.2
Max	26.5	26.8	27.3	23.0
N	103	72	71	134

Summary

The effect of Seroquel on weight change in the long-term is minimal. There does not appear to be any relationship between weight change and the dose of Seroquel.

APPENDIX D

Correspondence with regulatory agencies

APPLICATION FOR MARKETING AUTHORIZATION
-MR PROCEDURE

Seroquel (REF No NL/H/156/01-03)
Quetiapine Zeneca (Ref No NL/H/157/01-03)

Consolidates Response to Concerned Member States

November 1999

COUNTRY : SPAIN SPC Question number ES-7:

According to SPC, quetiapine was associated with weight gain predominantly during the early weeks of treatment but the results of controlled and uncontrolled trials showed a duration-related increase in the incidence of clinically significant weight increase. This issue should be clarified.

AstraZencea response:

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

The apparent inconsistency identified by the reviewer is driven by 2 distinct factors. Firstly, the 2 columns in Table 59 in the Clinical Data Summary (number [%] with >7% the baseline weight and total mean weight increase [kg], respectively) are not directly comparable. The total mean weight increases have been calculated using the *last value* for each patient within each time period. (These mean weight change also takes into account patients who lose weight). The other column, however, reports all patients who exceeded the 7% threshold *at any time* during the time period, including transient effects.

In order to clarify the situation, Table 7 presents the percentage of patients who experienced either a >7% weight increase or a >7% weight reduction by treatment duration(using an LVCF approach within each time period). In addition, the mean weight change by treatment duration is presented. (The data in Table 1 are based on the original data presented in the dossier).

Table 1 Weight data in patients treated with quetiapine in the Phase II/III controlled and uncontrolled trials

Treatment duration	N	% of patients			Mean weight change (kg)
		>7% reduction in weight	No significant change in weight	>7% gain in weight	
5 to 6 weeks	778	3.7	74.8	21.5	2.08
6 months	1190	12.0	62.9	25.0	0.76
12 months	573	13.8	50.9	35.3	1.59
>12 months	346	16.8	42.7	40.4	2.00

As can be seen in Table 7, at week 6 there is a marked imbalance between the percentage of patients who have experienced a >7% weight increase and reduction. This reflects the pharmacological effect of quetiapine. However, after this short-term effect, the increases in each category are more balanced reflecting the natural variability of weight across time.

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

APPLICATION FOR MARKETING AUTHORISATION

Response to comments made by the French Medicines Agency (FMA) in Annexe B of their letter dated 9 April 1998

June 1999

The uncertainty regarding the efficacy should be balanced with the undesirable effects, ie, hepatocytolysis (ALT > 5 x ULN in 0.4% of subjects), opacities on the lens, weight gain in 15% to 20% of subjects (2.8 kg in 6 months and 5 kg after 6 months) and neutropenia (4 to 5 per 1000).

AstraZeneca response (to weight gain):

The Commission commented that between 15% and 20% of patients had an increase in body weight of >7%. Table 6-8 provides data from the updated safety database.

Table 6-8 Magnitude of effect over time of quetiapine on weight gain in the Phase-II/III trials

Duration of exposure	Controlled trials (Mean duration 48.1 days)		Controlled and uncontrolled trials (Mean duration 164.4 days)	
	Number (%) with >7% the baseline weight	Total mean weight increase (kg)	Number (%) with >7% the baseline weight	Total mean weight increase (kg)
≤1 week	11 of 396 (2.8)	0.39	15 of 564 (2.7)	0.15
>1 to 2 weeks	38 of 475 (8.0)	0.67	45 of 661 (6.8)	0.64
>2 to 3 weeks	50 of 350 (14.3)	1.54	60 of 475 (12.6)	1.08
>3 to 4 weeks	48 of 338 (14.2)	1.65	62 of 495 (12.5)	1.20
>4 to 5 weeks	50 of 236 (21.2)	2.31	53 of 308 (17.2)	1.66
>5 to 6 weeks	164 of 727 (22.6)	2.19	167 of 778 (21.5)	2.08
>6 weeks to 6 months	61 of 289 (21.1)	1.55	337 of 1190 (28.3)	0.76
>6 to 12 months	34 of 66 (51.5)	5.15	229 of 573 (40.0)	1.59
>12 months	4 of 8 (50.0)	5.30	180 of 346 (52.0)	2.00
At any time	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

There was a duration-related increase in the incidence of clinically significant weight gain (>7% of baseline) in patients treated with quetiapine. The number of patients treated with quetiapine in the controlled and uncontrolled Phase-II/III trials who had an increase in body weight of >7% of baseline at any time during treatment (610 of 2216 [27.5%]) was higher than that at the end of

treatment (430 of 2216 [19.4%]), indicating that patients who had put on weight could subsequently lose it on continued quetiapine therapy.

The Commission commented that weight gain was 2.8 kg in the first 6 months and 5 kg after 6 months. Data from the updated safety database indicate that the mean greatest weight increase was 5 to 6 kg, and was higher in patients treated with quetiapine in the controlled trials compared with those in the combined controlled and uncontrolled trials. It should be noted that the number of patients in the controlled trials at the later time points is small, thus making it difficult to assess whether the increase in weight continues at the same rate or whether it slows after about 6 months.

Table 6-9 shows the mean weight increase and the incidence of clinically significant weight increases (>7% of baseline) by dose of quetiapine in the updated safety database.

Table 6-9 Number (%) of patients with clinically significant increase in body weight (>7% of baseline) by dose of quetiapine in the Phase-II/III trials

Dose of quetiapine	Controlled trials (Mean dose 342.3mg/day)		Controlled and uncontrolled trials (Mean dose 377.4mg/day)	
(mg/day)	Number (%) with >7% the baseline weight	Mean weight increase (kg)	Number (%) with >7% the baseline weight	Mean weight increase (kg)
<150	43 of 352 (12.2)	0.39	34 of 298 (11.4)	-0.18
≥150 but <300	51 of 276 (18.5)	1.51	129 of 466 (27.7)	1.37
≥300 but <450	95 of 498 (19.1)	1.49	169 of 623 (27.1)	1.30
≥450	106 of 422 (25.1)	2.23	274 of 822 (33.3)	0.09
Any dose	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

The mean weight change in patients in each group was small, although there was some evidence of a dose-related increase in incidence of patients gaining >7% of baseline in body weight.

In summary, these additional data confirm the findings in the original MAA and are consistent with the wording in the Summary of Product Characteristics, which states that treatment with quetiapine is sometimes associated with increases in body weight.

Response to the letter from the IKS (Interkantonale Kontrollstelle fur Heilmittel) dated 17 April 1997 concerning quetiapine tablets 25, 100 and 200 mg

September 1998

5 **The level of weight gain (22% of patients gained more than 7% in weight) was clearly higher than that observed for the standard preparation haloperidol. Sedation and autonomic, anticholinergic effects were more frequent than with the reference preparation. Where investigated, there was also a clear increase in serum cholesterol levels.**

5.1 Effect of quetiapine on weight gain

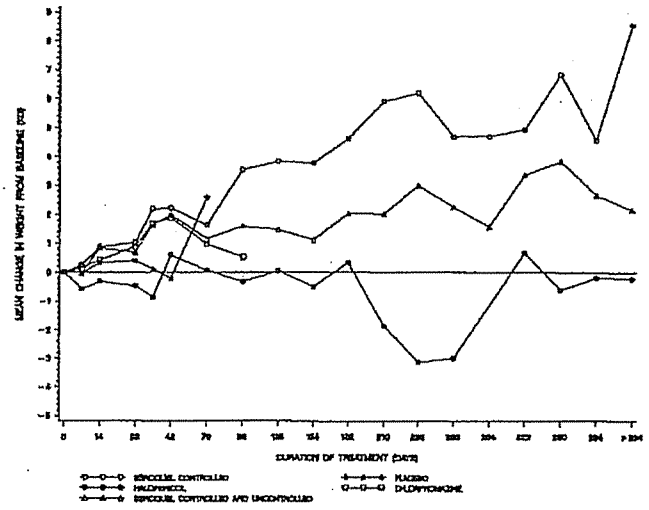
Supporting data are provided in the Supporting Documentation on the Safety of Quetiapine, Section 1.7.

As with most other antipsychotic agents - including recently approved agents such as olanzapine and risperidone - quetiapine was associated with weight gain.

The incidence of adverse events of weight gain in patients treated with quetiapine in the placebo-controlled trials was small (2.0% of 510) and lower than that in patients treated with olanzapine in similarly designed placebo-controlled trials (5.6% of 248). Patients treated with quetiapine in the placebo-controlled trials gained a mean of approximately 2 kg body weight, similar to that observed with olanzapine (2.8 kg; US Summary Basis of Approval for olanzapine).

The incidence of clinically significant weight increase (>7% of baseline) in patients treated with quetiapine in the Phase-II/III trials increased with time, suggesting that weight gain may be a manifestation of successful long-term treatment with quetiapine. Figure 2 shows the mean change in body weight over time in the Phase-II/III controlled and uncontrolled clinical trials.

Figure 2 Mean change in body weight by duration of therapy in the Phase-II/III trials



The proportion of patients who gained >7% body weight during quetiapine therapy appeared to increase with increasing dose; this may have been because patients tended to take high doses of quetiapine for longer periods than low doses.

The present wording in the section on 'Possible adverse reactions' in the Quetiapine SmPC adequately alerts the prescriber to the above findings in the clinical trials programme for quetiapine.

REPLY TO INSTRUCTIONS FROM IST MHW EVALUATION CENTRE (EC) HEARING

Seroquel 25/100 mg tablets

March 1999

Instruction 82

Make comments on a possible mechanism of hyperplasia of the glucagon-secreting cells in the pancreas and clinical relevance of this finding.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson et al 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate. In addition, the plasma prolactin levels did not increase in clinical studies. Therefore, the risk for human could be low.

References

Sorenson et al. Endocrinology 1995; 136: 4092-8.

Weinhaus et al. Endocrinology 1996; 137: 1640-9.

APPLICATION FOR MARKETING AUTHORISATION APPROVAL IN SWEDEN

Response to the Medical Products Agency's (MPA's) Assessment Report of 27 January 1997 concerning quetiapine (SEROQUEL™) tablets 25, 100 and 200 mg (Aspnr: 96-243, 96-244, 96-245)

February 1997

The mechanism of the hyperplasia of the glucagon secreting cells in the pancreas in the 1-year rat study should be discussed.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson and Stout 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate.