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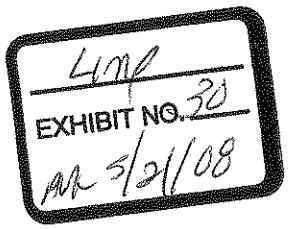
Date : Wednesday, July 5, 2000 4:26:00 PM GMT
From : Witch Emma E
To : Bache Ricky RA; Brecher Martin M; Devine Nancy NA; Duffy Paul PA - SAFA; Geller Wayne; Jones Martin AM - PHMS; Limp Gerald GL; Melvin Karen KS
Cc : DeFeo Pat PA; Fitton Lesley LR; Lindstrom Diane DD; Travers John JT
Subject : first draft of FDA response (part 2) for your review
Attachments : sugar response 3.doc
Custodians : Jones, Martin

From: Witch Emma E
Sent: 7/5/2000 8:56:41 AM
To: Brecher Martin M; Devine Nancy NA; Geller Wayne; Limp Gerald GL; Bache Ricky RA; Duffy Paul PA - SAFA; Jones Martin AM - PHMS; Melvin Karen KS
CC: Fitton Lesley LR; Lindstrom Diane DD; DeFeo Pat PA; Travers John JT
BCC:
Subject: first draft of FDA response (part 2) for your review



Dear All

Please find attached the first draft on the FDA response on diabetes (in response to question 2 of the request) for your review. Please accept my apologies for the delay in getting this to you.

It would be really useful if you could review the attached and bring any comments to the meeting on Thursday 6 July (3-5, 11F24 UK, 10-12 5A3-342 US).

I have kept the discussion section of the attached to a minimum, mainly because we are still waiting for some data and also because I think we need input from the medics here. However, I have read a couple of papers and have a few suggestions for the discussion section, as indicated in the attached.

I have not received any other contributions to this response yet. Please could you try and issue something in advance of our meeting on Thursday (at the latest), the purpose of which is to resolve any major issues before most of us attend the CINP in Brussels next week.

Many thanks

Emma

Answer to Part 2 of FDA request: draft

1.1 Source material

1.1.1 Adverse event data

The adverse event data and plasma glucose data provided below are from the Phase I , II and III trials in the Seroquel NDA.

Adverse events were categorised using an in-house dictionary based on the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). For the purpose of this FDA request, a list of COSTART terms for adverse events which are considered to have a possible relationship to disturbances in glucose metabolism have been identified. These are as follows:

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

The frequency of the above events have been summarised and assessed below.

1.1.2 Plasma glucose data

Mean changes from baseline in plasma glucose levels and the percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration in the placebo-controlled Phase II/III trials have been summarised and assessed below.

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

As the glucose levels assessed in the placebo-controlled Phase II/III trials were non-fasting values, a markedly abnormal plasma glucose concentration has been defined as a plasma glucose concentration equal to or greater than 200 mg/dl.

1.2 Results

1.2.1 Adverse event data

- **Total adverse events**

The incidence of all adverse events with a possible relationship to disturbances in glucose metabolism in the Phase I and Phase II/III studies are listed in Table 1.
<< Do we need to present results from the active controlled trials and the uncontrolled trials? If not, will remove from the table>>.

- **Deaths due to adverse events**

There were no deaths due to any of the adverse events in Table 1.

- **Withdrawals due to adverse events**

A total of 3 patients were withdrawn from treatment due to the adverse events in Table 1:

- 1 patient (0007/0708) was withdrawn due to weight gain
- 2 patients (0093/9304 and 0001/0109) were withdrawn due to hyperglycemia.

Full narratives of these 3 patients are provided in Appendix A.

- **Serious adverse events**

Apart from the 3 events leading to withdrawal from treatment (above), none of the other events in Table 1 were classed as serious by the Investigators.

1.2.2 Plasma glucose concentration data

- **Mean changes from baseline in plasma glucose levels**

<< to be inserted>>

- **Percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration**

<< to be inserted>>

Table 1 Incidence of adverse events possibly related to disturbances in glucose metabolism in the Phase I and Phase II/III trials

COSTART term	Number (%) of patients					
	Phase I trials	Controlled Phase II/III trials				Controlled and uncontrolled Phase II/III trials
	Seroquel (n=300)	Seroquel (n=1710)	Placebo (n=206)	Haloperidol (n=320)	Chlorpromazine (n=100)	Seroquel (n=2162)
Weight gain	1 (0.3)	31(1.8)	0	3 (0.9)	0	67 (3.1)
Thirst	0	4 (0.2)	0	0	0	5 (0.2)
Polyuria	1 (0.3)	1 (0.1)	0	0	1 (1.0)	2 (<0.1)
Urinary frequency	1 (0.3)	2 (0.1)	0	1 (0.3)	0	5 (0.2)
Diabetes mellitus	0	0	0	0	0	3 (0.1)
Hyperglycemia	1 (0.3)	0	0	0	0	2 (<0.1)
Hyperosmolar coma	0	0	0	0	0	0
Diabetes ketoacidosis	0	0	0	0	0	0

1.3 Discussion

No patients in the Phase I or Phase II/III trials had adverse events of hyperosmolar coma or diabetes ketoacidosis.

The incidences of all the other events in Table 1 were unremarkable, and the severity was such that only 3 patients in total were withdrawn from Seroquel treatment. Two subjects were withdrawn because of hyperglycemia (one was a known diabetic with a history of hyperglycemia before entering the trial and the other had a history of borderline elevated glucose levels). The third patient was withdrawn due to weight gain (and abdominal pain and somnolence); only in this latter case did the Investigator consider the event to be probably related to trial treatment. None of the other events in Table 1 were considered serious by the Investigator.

If including open label data:

A total of 3 patients treated with Seroquel (0.3%) had an adverse event of diabetes mellitus in the Phase II/III uncontrolled trials; none of the events were considered serious by the Investigators. Further details of these 3 patients are provided in Table X.

Table 2 Patients with diabetes mellitus in the Phase II/III uncontrolled trials

Subject	Adverse event as reported	Age	Sex	Total daily dose of Seroquel	Duration of treatment with Seroquel	Past history of diabetes?
0046/4603	Unstable diabetes	35	F	300	9	Yes
0036/3605	Diabetes mellitus	51	F	400	61	No
0005/0509	Poorly controlled diabetes mellitus	40	F	500	344	Yes

According to the past medical history of these 3 patients, it is clear that in 2 cases (0046/4603 and 0005/0509) the adverse event reported was an exacerbation of a pre-existing diabetic condition. In the remaining case (0036/3605) the patient is reported to have recovered from the diabetes whilst on Seroquel treatment and the incident was noted as not being related to Seroquel treatment. << *Could also look at conc meds in these patients, if considered necessary (alpha blockers, beta blockers, corticosteroids, cyclosporine, phenytoin, phenothiazines, thiazide diuretics and oral contraceptives all have the potential to impair glucose metabolism) and also mention that this incidence is much less than that expected in a schizophrenic population (15.8% has been reported)*>>

Further possible areas for discussion:

- Relatively high rates of diabetes have been observed in patients treated with clozapine and olanzapine. It is suggested that this may be a direct result of antagonism of 5-HT receptors, which leads to decreases in insulin levels and subsequent hyperglycemia. Does the Seroquel receptor profile differ substantially from that of clozapine and olanzapine, which may account for why we see high rates of diabetes in the latter but not with Seroquel. Thought that this may be useful for the discussion? If so, who on the team will be able to look into this?
- Further, it has been reported that prolactin induces an insulin-resistant state, necessitating elevated insulin levels to maintain normal glucose homeostasis. Perhaps we should therefore mention in the discussion that see very few disturbances in glucose metabolism with Seroquel which could in part be due to the fact that it does not cause prolactin elevations?
- Weight gain is a risk factor for diabetes and we have a relatively high rate of this in Table 1. Would we therefore need to address our incidence of weight gain in some detail and show, for example, that none of the patients with weight gain went on to develop diabetes in the trials?
- It has also been suggested that novel antipsychotics might induce diabetes by exacerbating existing disease or pre-disease, rather than by damaging previously normal homeostatic systems. Therefore, should we look at *all* those patients who have a past history of diabetes in our trials and show that not all of them (2 did) went on to develop worsening diabetes following seroquel treatment?

<< Discussion of glucose data to be inserted eg, did any of the patients with a markedly elevated glucose levels have any of the adverse events mentioned in Table 1 ie were they symptomatic >>

1.4 Conclusion

<< to be inserted>>

References

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

APPENDIX A: Patient narratives

5077IL/0012, Subject UK_0007/0708_(quetiapine)

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 quetiapine 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 quetiapine.

5077IL/0012 OLE, Subject 0093/9304_(quetiapine)

Hyperglycemia

This 53_year_old, white woman with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 34 (quetiapine 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, atenolol, insulin protamine injection, insulin regular, and drotaverine. On Day 18 (quetiapine 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 OLE, Subject 0001/0109_(quetiapine)

Hyperglycemia

This 44_year_old, black man with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 10 (quetiapine 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 21.8 mmol/L (normal range 3.8 to 6.4 mmol/L). A repeat level drawn on Day 8 was 22.6 mmol/L. 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 (quetiapine 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 61.3 mmol/L. 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 11 mmol/L 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 11 mmol/L 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.

FDA response (Part 2)
Draft 1
05/06/00