EXHIBIT 30

Objection Handler on
Atypical antipsychotics and glucose dysregulation

By Dr Richard Owen
Global Medical Affairs Manager-Seroquel

With contributions from: Rebecca Bowen (Global Brand Director)
Dr Chip Altman (Global Commercial Physician)
Alison Wilkie (Global Communications Manager

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Summary

- **The literature contains much conflicting information concerning the prevalence of diabetes and glucose dysregulation with atypical antipsychotics. Most of the published evidence relates to clozapine and olanzapine.**

- **Product labels vary widely between countries concerning statements about diabetic risk-not only between products but for the same product in different countries.**

- **The company's safety database has reassuring data concerning Seroquel's diabetic potential and glucose regulation**

Background

Abnormalities in glucose regulation including diabetes mellitus can occur more commonly in schizophrenia patients compared with healthy individuals; a phenomenon which has been recognised even prior to the neuroleptic era. Hyperglycaemia, exacerbation of existing diabetes, new onset type 2 diabetes and diabetic ketoacidosis have been reported with a variety of atypical agents but the vast majority of reports are with clozapine and olanzapine.

This objection handler summarises the key publications in the literature to date, label statements and changes with our main competitors and summarises our data with Seroquel regarding diabetes and glucose dysregulation.

Summary of selected published data

A recent review by Henderson (CNS Drugs 2002; 16 (2): 77-89) reviews the evidence for atypical antipsychotic-induced diabetes mellitus.

Henderson.pdf

In summary their main conclusions was that most of the evidence of diabetogenic risk relates to clozapine and olanzapine. However the topic is complex and the literature is full of both supportive or dismissive evidence concerning the risk of hyperglycaemia and diabetes with atypicals. Only controlled trials will lead to a fuller understanding and such trials are at present uncommon.

It is interesting to note the different approaches by the various companies in relation to their antipsychotic. The approaches can be broadly summarised as follows:

Lilly- have tried to imply that diabetes/glucose dysregulation is a <u>class effect</u> of atypicals (in other words if olanzapine is going to be singled out as a culprit they intend to brand all the atypicals as guilty as well)!

Janssen and *Pfizer*- tried to imply that risperidone and ziprasidone are different to other atypicals in that it cause little or no problems with diabetes or glucose regulation. (Data cited in Henderson 2002). Moreover risperidone has been used without complications in patients with schizophrenia and comorbid diabetes.

BMS- have published retrospective audits showing that olanzapine and risperidone are associated with increased diabetic risk compared to typicals (but surprisingly did not mention their own drug aripiprazole in this audit).
See e.g. BMJ article by Koro et al 2002-11-22
Koro et al 2002
They have shown relatively little data on aripiprazole and glucose levels although data on fasting blood glucose levels from a 26 week study did not reveal any problems (see CME slide no.58 in Key Claims section in the aripirazole pyramid).
http://cns.ta.astrazeneca.net/pyramids/Aripiprazole/aripiprazole_Claims.htm

AZ- We have presented data on an audit by Gianfrancesco et al showing that the risk with olanzapine is greater than the risk with Seroquel, risperidone and conventional antipsychotics.
Gianfrancesco et al 2002
There are data from Reinstein et al (Clin Drug Invest. 1999; 18: 99-104) showing that the addition of Seroquel to a clozapine regime improved glucose metabolism in 20% of the 13 patients who developed diabetes on clozapine alone. We currently await the results of study 43 which will compare fasting blood glucose levels between Seroquel and risperidone.

A selection of recent literature on diabetes and antipsychotics is attached.


Rev-lit-diab.doc

Label statements/changes that have occurred for Seroquel and the competition

(a) Japan

Recently the Japanese regulatory authorities imposed label changes relating to diabetes and glucose dysregulation for both Zyprexa (in April 2002) and Seroquel(in November 2002). These essentially comprise a contraindication for these agents in patients with diabetes or a history of diabetes and a requirement for blood glucose monitoring. The attached icon contains details of the letter that was sent to clinicians in Japan explaining the change to the labelling.


Sero-japdeardr.doc

Risperidone recently had the word 'hyperglycaemia' added to the other ADR's section of its label in Japan. Clozapine aripiprazole and ziprasidone are not yet marketed in Japan.

(b) US

The table below gives the current US PDR classification of glucose related adverse events for marketed /soon to be marketed atypicals.

	Adverse event frequency	
Product	**Infrequent (0.1-1%)**	**Rare (<0.1%)**
Seroquel	Hyperglycaemia Diabetes mellitus	
Olanzapine	Diabetes mellitus Hyperglycaemia	
Aripiprazole	Diabetes mellitus Hyperglycaemia	
Risperidone	Diabetes mellitus	
Ziprasidone	Hyperglycaemia	Glucose tolerance decreased
Clozapine	Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of CLOZARIL® (clozapine) should be considered. Hyperglycaemia (<1%)	

(c) Europe

Seroquel

EU – the Pharmacovigilance Working Party of the CPMP reviewed the class in June 2001. Seroquel SmPC has language "Special Warnings and Precautions for Use" section stating that hyperglycaemia and exacerbation of preexisting diabetes has been reported in very rare cases and that appropriate clinical monitoring is advisable. Similar wording is also in the Undesirable Effects section.

In UK, discussions regarding these issues are pending with MCA and should be resolved by the end of the year

The Italian label includes warnings and precautions that hyperglycaemia and the exacerbation of pre-existing diabetes have been reported rarely, and that monitoring is advisable.

Olanzapine

The EU label for olanzapine states that elevated glucose levels are common (frequency 1-10%). In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels <7.8 nmol/l the incidence of non-fasting plasma glucose levels >11nmol/l (suggestive of diabetes) was 1.0% compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels >8.9nmol/l but <11mmol/l (suggestive of hyperglycaemia) was 2.0% compared to 1.6% with placebo. Hyperglycaemia is also reported as a very rare (<0.01%) spontaneous event.

Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Risperidone

The EU Pharmacovigilance Party of the CPMP has proposed similar wording to that for Seroquel mentioned above.

The current UK label makes no mention of diabetes or hyperglycaemia for risperidone.

Ziprasidone

From the Swedish label:

In a double-blind comparative study, metabolic parameters were measured including weight, fasting insulin, total cholesterol, triglycerides and an insulin resistance (IR) index. Among patients receiving ziprasidone no significant changes from baseline values were observed for any of these metabolic parameters".

Clozapine
From the UK SmPC:
Abnormalities of glucose homeostasis occur uncommonly in approximately 0.35% of CLOZARIL (clozapine) patients in the UK cohort monitored by the CLOZARIL Patient Monitoring Service. Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL (clozapine) treatment in patients with no prior history of hyperglycaemia. Blood glucose levels normalised in most patients after discontinuation of CLOZARIL (clozapine), and a rechallenge in a few cases produced a recurrence of hyperglycaemia. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL (clozapine) particularly if symptoms of polydipsia, polyuria, and weakness develop. With prolonged treatment considerable weight gain has been observed in some patients and further investigation is periodically needed to ensure hyperglycaemia is not missed. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL (clozapine) should be considered when active medical management of the hyperglycaemia has failed.

Seroquel safety database analysis

Note: This summary has been adapted from a review of the company database and since adverse event data constantly changes only qualitative conclusions have been presented here.

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

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

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

- Worldwide (including Japan) postmarketing reports comprise cases of new-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, diabetic ketoacidosis or hyperglycaemia. However, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. This position is supported by the literature where the incidence of diabetes mellitus in the schizophrenic population is noted to exceed that in the general population, even prior to the introduction of atypical antipsychotic medications (Dixon L et al 2000; Schiz Bull.26 (4):903-912).

Company position

Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.

There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes.

There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.