# Hyperglycaemia Labelling

US / FDA Position

The FDA have recently (11 September, 2003) issued letters to the concerned companies requesting them to include hyperglycaemia / diabetes class labelling for the following atypical antipsychotics

- Zyprexa (olanzapine)
- Clozaril (clozapine)
- Risperdal (risperidone)
- Seroquel (quetiapine)
- Geodon (ziprasidone)
- Abilify® (aripiprazole).

The FDA action has been generally in response to increased publicity, but specifically in response to the results of the Cunningham / VA (Veterans' Association) study, preliminary results of which were published in a poster at APA. The PI wording reads requested by FDA reads as follows:

***WARNINGS***

***Hyperglycemia and Diabetes Mellitus***

*Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Zyprexa. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.*

*Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.*

We understand that Pfizer and BMS intend to oppose this wording for ziprasidone and aripiprazole respectively.

**European position**

We will disclose the FDA class wording information appropriately to CPMP via the periodic safety update report (PSUR) to be submitted 30 November.

The CPMP Pharmacovigilance Working Group (PhVWG) have recently concluded a review of hyperglycaemia / diabetes labelling for four of these antipsychotics (olanzapine, clozapine, risperidone, quetiapine). This review, led by the Swedish Regulatory Authority (MPA), began in April 2000 and was only completed at the July 2003 CPMP meeting.

The CPMP have decided on different SPC wording for the four products, which they propose should be implemented across all EU countries.

***Zyprexa***
***Section 4.4. Special warnings and precautions for use***
*Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus.*

***Section 4.8 Undesirable effects***
*In the Table on clinical trial events:*
*Metabolism and nutrition disorders: Common (1-10%): Elevated glucose levels (see note 1 below).*
*Note 1: In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels 7.8 mmol/l, the incidence of non-fasting plasma glucose levels 11 mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels 8.9 mmol/l but < 11 mmol/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.*

*In the Table on spontaneous events:*
*Metabolism and nutrition disorders: Very rare (<0.01%): Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also Note 1 above and section 4.4).*

***Clozapine***

*Section 4.4. on Special warnings and precautions for use*
*Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus may occur during treatment with clozapine (see also section 4.8). Severe hyperglycemia with ketoacidosis or coma has been reported in very rare cases, some of which have been fatal. Appropriate clinical monitoring is advisable, especially in diabetic patients and in patients with risk factors for the development of diabetes mellitus. Where follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the glucose impairment, and reinstitution of clozapine has resulted in reoccurrence of glucose impairment.*

*Section 4.8 on Undesirable effects*
*In the table under Metabolic*
*Common undesirable effects: Weight gain, impaired glucose tolerance, diabetes mellitus*
*Very rare undesirable effects: Severe hyperglycemia, diabetic acidosis.*

***Quetiapine***

*Section 4.4. on Special warnings and precautions for use*
*Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during quetiapinee treatment. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.*

*Section 4.8 on Undesirable effects*
*Hyperglycaemia or exacerbation of pre-existing diabetes mellitus has been reported in very rare cases..*

***Risperidone**:*

*Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects*
*Hyperglycaemia or exacerbation of pre-existing diabetes mellitus has been reported very rarely.*

Because of the different approval systems in Europe the new wording will be implemented in different ways for the four products. For Zyprexa, the wording will be implemented throughout the European Union as part of the centralised approval for the bipolar recurrence prevention indication. For Seroquel, the wording has already been adopted in many countries and is likely to be enforced via a mutual recognition label change, possibly with the bipolar mania approval if they achieve that. As risperidone and clozapine are older products and are nationally licensed (i.e. each country may have a different SPC), the CPMP edict has to be implemented by national authorities, using national procedures. Implementation may thus be variable and slow in some countries. We therefore ask regulatory staff in the affiliates to monitor the hyperglycaemia / diabetes wording in the risperidone SPCs in EU.

Important note: The CPMP hyperglycaemia / diabetes wording proposals are not in the public domain and will not enter the public domain from CPMP. We, Lilly, therefore have to be very careful how we use the information above.

As stated above, we will disclose the FDA class wording information appropriately to CPMP via the periodic safety update report (PSUR) to be submitted 30 November. However, as CPMP have just taken 3½ years to come up with their present proposals, they are unlikely to reconsider the issue of hyperglycaemia again in the near future, particularly in response to industry prompting. We should also note that the FDA wording is more extensive than current EU labelling, and efforts to use this to “level the playing field” in Europe, may only serve to raise / maintain the profile of this issue.

It is also my belief that based on their general awareness and also the monthly phone conferences on safety / drug matters, that CPMP will be well informed as to the FDA action on this topic.

**The proposed regulatory actions at this time are:**

1. Regulatory staff in all affiliates to monitor the labelling of the competitor products (risperidone, quetiapine, ziprasidone) on a regular basis (at least once per month).
2. PSUR12 and the covering letter include specific information about the Cunningham VA study and the US FDA labelling change. These should be submitted (per normal practice) to all EU national regulatory agencies.

3. All affiliates to follow up the PSUR12 submission in writing, by phone or informally in conversation as and when opportunities arise, drawing specific attention to the FDA class labelling on hyperglycaemia.

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