Rapporteur's Revised Assessment Report

Zyprexa/Olansek/Zyprexa Velotab

Review of the Data on Olanzapine and Risk of Diabetes Mellitus

Rapporteur: Finland, Dr Markku Toivonen
Assessor: Dr Tapio Kuitunen, Dr Markku Toivonen
Date of AR: 17 January 2003
Date of revision: *14 February 2003*

1. Introduction

As requested by the CPMP and PhVWP on September 2002, the MAH has submitted the following documents regarding olanzapine and diabetes for review:

- Olanzapine and the Relative Risk of Diabetes Mellitus
- Impact of diabetes related SPC Special Warnings and Special Precautions Changes on Reporting Rates of Hyperglycaemic Events
- Briefing Document on Olanzapine and Glucose Homeostasis. An earlier version of this document has also been submitted to the FDA in October 2002

The changes regarding hyperglycaemia made to the SPCs for Olanzapine from September 1996 through the present are shown in the Table 1.

Table 1. Hyperglycaemia and related disorders in the Olanzapine EU SPCs

Submitted	Approved	Section 4.4 Special warnings and special precautions for use:	Section 4.8 Undesirable effects:
23/12/98	19/07/99	Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during ZYPREXA treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	**Rare (<1%):** Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also Section 4.4, Special warnings and special precautions for use).
19/06/00	28/12/00	*Text moved to top of section and modified:* Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal	**Common (1-10%):** Non-fasting plasma glucose levels ≥ 11 mmol/l (suggestive of diabetes) as well as non-fasting levels ≥ 8.9 mmol/l but < 11 mmol/l (suggestive of

		cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	hyperglycaemia) in patients with baseline non-fasting glucose levels ≤ 7.8 mmol/l have been seen occasionally in clinical trials. Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also Section 4.4, Special warnings and special precautions for use).
05/12/00	14/06/01	*No change*	**Common (1-10%):** 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. For further information, see Section "Very Rare (<0.01%)" below. **Very Rare (<0.01%)**: Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also Section 4.4, Special warnings and special precautions for use).
Renewal 22/05/01	20/11/01 (Currently approved)	*No change*	*Information put into two tables:* The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials. **Metabolism and nutrition disorders** *Common (1-10%):* Elevated glucose levels (see note 1 below). [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. The following table of undesirable effects is based on post-marketing spontaneous reports. **Metabolism and nutrition disorders** *Very rare (<0.01%):* Hyperglycaemia or

			exacerbation of pre-existing 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, Special warnings and special precautions for use).

2. Olanzapine and the relative risk of diabetes mellitus

2.1 Case Reports

The MAH has performed a systematic search of the literature for the period from May 2000 through September 2002, which revealed a total of 84 published case reports of glucose dysregulation occurring in temporal association with atypical antipsychotic drug treatment. 49 of these cases were related to olanzapine, 27 to clozapine, 4 to risperidone, 3 to quetiapine, and 1 to ziprasidone. The reports deal with exacerbation of pre-existing diabetes, *de novo* diabetes, and acute presentations of diabetes (diabetic ketoacidosis or hyperglycaemic hyperosmolar coma).

According to the MAH, most of the patients had risk factors for diabetes mellitus in addition to the antipsychotic drugs listed above and including family history, obesity, comorbid illness and/or concomitant medications. The MAH concludes that these cases are not reported systematically and confounding data may be have been omitted from reports. Case reports are insufficient to determine the causality of the incidence of diabetes. These limitations have prompted researchers to undertake cohort studies.

2.2 Cohort Studies

The MAH reviews briefly the largest cohort studies on the risk of developing diabetes mellitus in patients taking or not taking antipsychotic drugs reported to date.

Sernyak et al (2002) investigated concomitant diabetes mellitus in 38,632 US Veterans Administration patients with schizophrenia treated with typical or atypical antipsychotic drugs during a 4-month period. A concomitant diagnosis of diabetes mellitus was significantly more likely in patients, especially younger patients less than 40 years old, taking atypical antipsychotic drugs when compared with those taking typical agents (9% greater risk, OR =1.09; 95% CI=1.03-1.15; p=.002). The odds ratios for the comparison between the four atypical agents investigated (clozapine, olanzapine, quetiapine, and risperidone) and typical antipsychotic drugs were similar (Figure 1.).

Methodological limitations of the study by Sernyak et al. (2002) include the narrow time frame (4 months) during which incident cases of diabetes were identified, lack of information on body weight, the potential for less compliance to treatment in the conventional antipsychotic group due to their less favourable side-effect profile, and the use of ICD-9 codes contained in an administrative database to identify cases of diabetes. Also, patients receiving atypical antipsychotic drugs were markedly different

from those receiving conventional agents in terms of comorbid psychiatric diagnoses (more prevalent among patients receiving atypical antipsychotics) and days of hospitalisation (2 to 3 times greater among patients receiving atypical antipsychotics).

The MAH concludes that it is difficult to determine the extent to which the observed results may reflect differences in patient characteristics that were not accounted for in the analysis, including greater chronicity or acute psychiatric illness severity in patients receiving atypical agents.

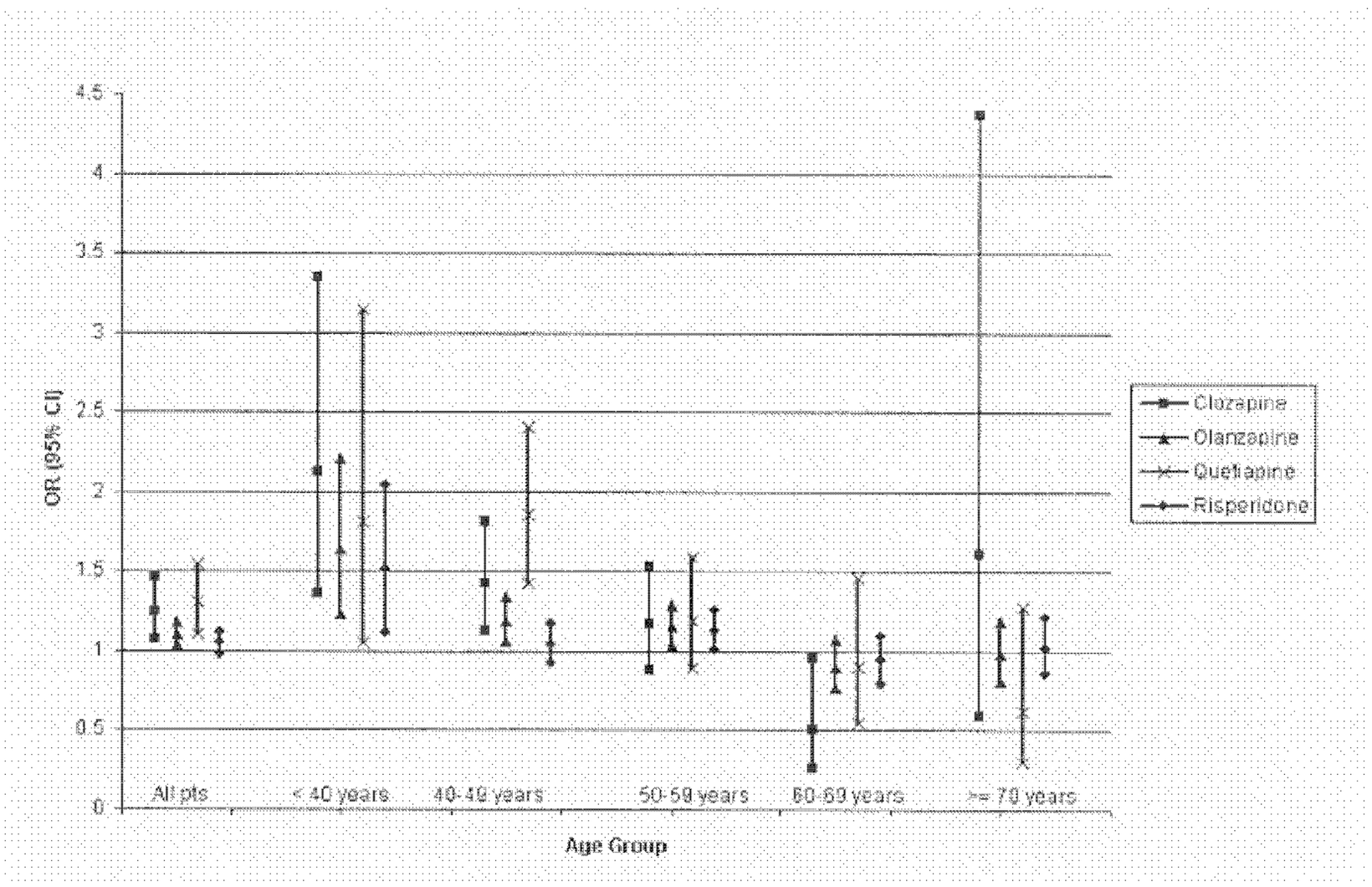

Figure 1. Prevalence of diabetes in schizophrenia: odds ratios during treatment with atypical compared with conventional antipsychotics.

Caro et al (2000) retrospectively investigated the odds ratios for having diabetes mellitus diagnosed in 33,945 patients registered with the Regie de l'Assurance Maladie de Quebec and treated with either risperidone or olanzapine. Patients treated with both olanzapine and risperidone were assigned to the olanzapine cohort. There was no significant difference between olanzapine and risperidone treated patients in the risk of developing diabetes during treatment (crude OR 1.08, CI=0.89-1.31). However, the risk ratio for female olanzapine treated patients was significantly greater than for female risperidone treated patients (HR 1.31, CI=1.05-1.65).

Gianfrancesco et al (2001) investigated the odds ratios for developing diabetes in 4,334 patients in the US treated with typical or atypical antipsychotic drugs during a normalised 12-month period. The risk of developing diabetes mellitus was significantly increased in patients treated with typical antipsychotic drugs, clozapine or olanzapine, (but not risperidone), when compared with patients who were not treated with antipsychotic drugs. They therefore concluded that clozapine and olanzapine were significantly more likely to be associated with diabetes mellitus than risperidone although the confidence intervals for clozapine and olanzapine overlapped those of risperidone.

Lund et al (2001) compared the incidence of diabetes in 3,013 schizophrenic patients in the US (Iowa) treated with either clozapine or typical antipsychotic drugs and reported no significant overall difference, although the incidence rate of diabetes was significantly increased in patients aged 20 to 34 years (RR = 2.5).

Comments of the MAH: Data from these cohort studies suggest that patients taking antipsychotic drugs, and especially perhaps atypical antipsychotic drugs, may be at an increased risk of developing diabetes mellitus. Finally, these data do not appear sufficient to support any conclusions regarding the differences in the incidence of diabetes between patients treated with atypical antipsychotic medications.

2.3 Case Control Studies and Retrospective Cohort Studies

The largest case control studies undertaken to date have utilized the UK General Practice Research Database or the Advance PCS Database.

UK General Practice Research Database (GPRD)

The UK GPRD has been interrogated by **Kornegay et al, Koro et al and Cavazzoni et al**.

Kornegay et al. (2002) identified 73,428 patients in the UK GPRD database treated with antipsychotic drugs between January 1994 and December 1998. The 424 patients with diabetes mellitus from this group were then each matched to 4 controls. Of patients exposed to antipsychotic drugs in the 6 months preceding the study, 152 were taking typical and 8 atypical (5 risperidone, 3 olanzapine) antipsychotic drugs. Of patients exposed to antipsychotic drugs in the 7-12 months preceding the study, 26 were taking typical and none were taking atypical antipsychotic drugs. The adjusted odds ratios for use of antipsychotic drugs (atypical and typical combined) in the 6 months preceding the study when compared with no use of antipsychotic drugs in the year preceding the study among patients with diabetes mellitus was 4.7 (CI=1.5-14.9) and 1.7 (CI=1.2-2.3), respectively.
The authors concluded that

- There is an increased risk of diabetes mellitus in patients taking atypical and typical antipsychotic drugs which is independent of other risk factors
- Numerically larger odds ratio observed among users of atypical antipsychotics should be viewed as preliminary, because the current atypical antipsychotic use group contained very few incident cases of diabetes.

Koro et al. (2002) identified 19,637 patients with schizophrenia in the UK GPRD database treated with antipsychotic drugs between June 1987 and September 2000. Patients with diabetes mellitus diagnosed $\geq$ 6 months after the start of the study from this group (229 of 18,443 taking typical antipsychotic drugs, 7 of 970 taking olanzapine and 7 of 1,683 taking risperidone) were each matched to 6 controls. Patients taking typical antipsychotic drugs had a significantly increased risk of developing diabetes mellitus compared to those not taking antipsychotic drugs (odds ratio: 1.4; CI=1.1-1.7). Patients taking olanzapine had a significantly increased risk of developing diabetes mellitus compared to those taking typical antipsychotic drugs (odds ratio: 4.2; CI=1.5-12.2) and those not taking antipsychotic drugs (odds ratio: 5.8; CI=2.0-16.7). Patients taking risperidone did not have a significantly increased risk of

developing diabetes compared to those taking typical antipsychotic drugs (odds ratio: 1.6; CI=0.7 –3.8) and those not taking antipsychotic drugs (odds ratio: 2.2; CI=0.9-5.2). This study may be criticised on the grounds that it was not powered to compare the odds ratios between patients taking olanzapine and risperidone and that the results of the study represent an arbitrarily selected and questionably representative 3-month period within a 3-year study.

Lilly (Cavazzoni et al. 2002) have undertaken an analysis of the UK GPRDatabase in order to determine the hazard ratio (HR) of diabetes mellitus in patients prescribed and not prescribed antipsychotic drugs. The patient groups studied included 46,111 who had received a prescription for a typical or atypical antipsychotic drug and 269,049 control subjects who had received ≥1 prescription for medication other than an antipsychotic drug between January 1996 and December 1997 inclusive. Patients with diabetes mellitus were defined as those with either a recorded diagnosis or who were prescribed any antidiabetic treatment. Patients taking any antipsychotic drug had a higher risk of developing diabetes mellitus than control subjects (HR=1.5; CI=1.1-1.9; p=.007) and those taking atypical antipsychotic drugs were at greater risk of diabetes mellitus than those taking typical antipsychotic drugs (HR=2.6; CI=1.3-5.3). Patients taking risperidone (HR=3.2; CI=1.4-7.1; p=.006) and thioridazine (HR=1.5; CI=1.009-2.3; p=.045) but not those taking olanzapine (HR=2.0; CI=0.3-14.5; p=.48) had a higher risk of developing diabetes than control subjects. However, the total numbers of patients taking these drugs was modest (risperidone = 1,702, olanzapine = 528).

Advance PCS Database

Buse et al. (2002) investigated the risk of developing diabetes mellitus in 38,969 patients treated with atypical and 19,782 treated with typical antipsychotic drugs registered in the Advance PCS database. Treatment with both typical (HR=3.5; CI= 3.1-3.9) and atypical (HR=3.1; CI=2.9-3.4) antipsychotic drugs was temporally associated with a significantly increased risk of developing diabetes mellitus. Treatment with risperidone (HR=1.23; CI=1.01-1.5) but not with olanzapine (HR=0.9; CI=0.76-1.07) was associated with a significantly increased risk of developing diabetes mellitus compared to treatment with haloperidol.

New Jersey Medicaid Database

Wang et al. (2002) investigated the risk of developing diabetes mellitus in patients from the New Jersey Medicaid program treated with clozapine by comparing 7,227 patients with newly treated diabetes and 6,780 control subjects. Clozapine was not associated with a significantly increased risk of developing diabetes mellitus (odds ratio: 0.98; CI=0.74-1.31) but both chlorpromazine (odds ratio: 1.31; CI=1.09-1.56) and perphenazine (odds ratio: 1.34; CI=1.11-1.62) were.

Analyses based on the UK GPRD are limited by the small number of patients treated with atypical antipsychotic drugs included in the Database and the inconsistent recording of information on risk factors for diabetes mellitus. Furthermore the Kornegay et al, Koro et al and Cavazzoni et al reports differ in the periods (1994 – 1998, an undefined three month period between 1997 – 2000 and 1996 – 1997 respectively), diagnosis (any patient taking an antipsychotic drug, schizophrenia and any patient taking an antipsychotic drug respectively) and numbers of individuals investigated which confounds comparison of their somewhat differing results.

Conclusions of the MAH: Taken together however, it seems reasonable to conclude that interrogation of the UK GPRD, the Advance PCS and other databases provides evidence that the risk of diabetes mellitus is greater in patients taking antipsychotic drugs than in control patients not taking antipsychotic drugs the risk of diabetes mellitus may be greater in patients taking atypical antipsychotic drugs than in patients taking typical antipsychotic drugs. These conclusions have been further addressed by post-marketing pharmacovigilance surveys.

3. Post-Marketing Pharmacovigilance Surveys

3.1 Clintrace Database

The MAH has identified a total of 907 possible cases of hyperglycemia or diabetes mellitus temporally associated with olanzapine treatment up to 31 March 2002, by which time approximately 9,070,000 patients had been treated with commercially marketed olanzapine (0.01% or 907 of 9,070,000). These reports were stratified into 716 that did not involve death, coma or acidosis and 191 that did involve death, coma or acidosis. A definite (n=54) or possible (n=88) cause of impaired glucose homeostasis other than olanzapine (such as significant risk factors for diabetes and concurrent medical disorders or treatments known to affect glucose homeostasis) was present in 142 of the latter 191 cases. Concurrent medical disorders, baseline risk factors, lack of information to base etiology or treatments known to affect glucose homeostasis were identified in all patients comprising the 48 deaths associated with definite glucose dysregulation that were identified from the 191 cases. In 66.7% (32/48) of these cases the reported cause of death was either not related to diabetes or glucose dysregulation, or was unknown.

No cause other than olanzapine was evident in 2 non-fatal cases out of the 191, both of which resolved on discontinuation of olanzapine. Hyperglycemia, baseline risk factors and ketoacidosis were reported in the first patient in whom concurrent medical disorders or treatments known to affect glucose homeostasis were not reported. Pancreatitis and ketoacidosis were reported in the second patient whose laboratory values were lipase 2399 U/L, amylase 577 U/L, triglycerides 1441 mg/dL, peak blood glucose 517 mg/dL. This patient had a history of dyslipidemia and was reported as non-compliant with olanzapine.

3.2 FDA MedWatch Database (Table 2.10)

The MAH queried the FDA MedWatch database for spontaneous adverse events suggestive of glucose dysregulation reported during treatment with clozapine, olanzapine, risperidone, quetiapine and ziprasidone to the end of September 2001. Probable glucose dysregulation had been reported during treatment with all currently available atypical antipsychotic drugs, the absolute total number of reported events being greatest for olanzapine, followed in order by clozapine, risperidone, quetiapine, and ziprasidone. When patient-years exposures are considered the highest reporting rate is observed for clozapine, followed by ziprasidone, olanzapine, quetiapine and risperidone. When only potentially severe glucose dysregulation events were considered reporting rates decreased from clozapine through olanzapine, quetiapine, and risperidone.

The observed differences in reporting rates among patients treated with atypical antipsychotics must be interpreted within the context of the known limitations of spontaneous report data, including the

approximation of drug exposures on the basis of prescription data and potential differences in reporting practices and reporting environment. Given these limitations, it is not possible to resolve whether the differences in reporting rates of the magnitudes observed in these analyses reflect a substantial difference in the actual incidence or prevalence of events at the population level.

Table 2.10. Reporting Rate (Per 100,000 Patient-Years) for All Glucose Dysregulation-Related Reports FDA MedWatch Database through 30 September 2001

	Clozapine[a]		Olanzapine		Quetiapine		Risperidone		Ziprasidone	
MedDRA Preferred Term	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate	Freq	Reporting Rate
Diabetic ketoacidosis	31	1.51	72	1.94	11	1.47	13	0.20	0	0.00
Ketoacidosis	31	1.51	32	0.86	1	0.13	18	0.27	0	0.00
Ketonaemia present	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00
Ketonuria present	5	0.24	5	0.13	3	0.40	1	0.02	0	0.00
Metabolic acidosis NOS	7	0.34	14	0.38	7	0.93	8	0.12	0	0.00
Lactic acidosis	1	0.05	9	0.24	1	0.13	7	0.11	0	0.00
Blood lactic acid increased	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00
Acetonaemia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Acetone increased	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Acetone	0	0.00	1	0.03	0	0.00	0	0.00	0	0.00
Acidosis NOS	9	0.44	5	0.13	1	0.13	9	0.14	0	0.00
Blood pH decreased	0	0.00	2	0.05	0	0.00	1	0.02	0	0.00
Nonketotic hyperglycaemic-hyperosmolar coma	0	0.00	4	0.11	0	0.00	0	0.00	0	0.00
Diabetic hyperosmolar non-ketoacidosis	2	0.10	1	0.03	0	0.00	0	0.00	0	0.00
Diabetic hyperosmolar coma	0	0.00	3	0.08	0	0.00	0	0.00	0	0.00
Diabetic hyperglycaemic coma	4	0.19	2	0.05	1	0.13	0	0.00	0	0.00
Diabetic coma NOS	12	0.58	10	0.27	1	0.13	2	0.03	0	0.00

(continued)

Table 2.10. Reporting Rate (Per 100,000 Patient-Years) for All Glucose Dysregulation-Related Reports FDA MedWatch Database through 30 September 2001 (concluded)

	Clozapine[a]		Olanzapine		Quetiapine		Risperidone		Ziprasidone	
MedDRA Preferred Term	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**	**Freq**	**Reporting Rate**
Diabetes mellitus insulin-dependent	16	0.78	5	0.13	0	0.00	2	0.03	0	0.00
Diabetes mellitus non insulin-dependent	27	1.31	10	0.27	2	0.27	4	0.06	0	0.00
Gestational diabetes	1	0.05	4	0.11	0	0.00	0	0.00	0	0.00
Diabetes mellitus NOS	143	6.96	63	1.70	11	1.47	54	0.82	1	3.45
Diabetes mellitus aggravated	17	0.83	11	0.30	2	0.27	13	0.20	2	6.90
Diabetes mellitus inadequate control	0	0.00	6	0.16	0	0.00	6	0.09	0	0.00
Glycosuria present	6	0.29	4	0.11	0	0.00	4	0.06	0	0.00
Glucose urine	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Glycosylated haemoglobin increased	1	0.05	3	0.08	0	0.00	0	0.00	0	0.00
Diabetic complication NOS	0	0.00	1	0.03	0	0.00	0	0.00	0	0.00
Hyperglycaemia NOS	71	3.45	128	3.45	10	1.34	92	1.40	1	3.45
Blood glucose increased	8	0.39	34	0.92	6	0.80	7	0.11	1	3.45
Blood glucose abnormal	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00
Glucose tolerance decreased	0	0.00	0	0.00	0	0.00	3	0.05	0	0.00
Glucose tolerance impaired	2	0.10	1	0.03	0	0.00	0	0.00	0	0.00
Insulin resistance	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood insulin decreased	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Totals	**395**	**19.22**	**434**	**11.70**	**57**	**7.61**	**244**	**3.72**	**5**	**17.24**
Total Patient-Years Exposure	***2,055,000***		***3,708,000***		***749,000***		***6,565,000***		***29,000***	

Abbreviations: Freq = number of events; NOS = not otherwise specified.

[a] Only clozapine reports included from 1 Jan 1996 thru 30 Sep 2001, as clozapine utilization data was not available to Lilly for the period prior to 1 Jan 1996.

Note: Reports manually reviewed and duplicate reports were removed

Note: Reporting rate = frequency / total patient-years exposure x 100,000

The FDA have published MedWatch data on reports of clozapine-, olanzapine- and risperidone-associated diabetes mellitus (Koller et al, 2001, 2002 and 2002) as follows:

- 384 reports of clozapine-associated diabetes mellitus (exacerbation of current disease 54 cases, new onset disease 242 cases, metabolic acidosis or ketosis 80 cases and 15 fatal cases) from January 1990 through February 2001
- 237 reports of olanzapine-associated diabetes mellitus (exacerbation of current disease 44 cases, new onset disease 188 cases, metabolic acidosis or ketosis 80 cases and 25 fatal cases) from January 1994 through May 2001
- 132 reports of risperidone-associated diabetes mellitus (exacerbation of current disease 40 cases, new onset disease 83 cases, metabolic acidosis or ketosis 36 cases and 5 fatal cases) from January 1993 through December 2001

The MAH concludes that the FDA MedWatch database provides evidence that glucose dysregulation has been reported during treatment with all widely available atypical antipsychotic drugs but does not address causality or potential differences between individual atypical antipsychotic drugs for risk of glucose-dysregulation events. These issues have been examined in a number of pathophysiological investigations.

4. Pathophysiological Investigations

Pathophysiological investigations have examined the effects of antipsychotic drugs on cultured pancreatic cells or have evaluated the results of glucose challenges in patients receiving treatment with antipsychotic drugs for major mental illnesses. However, studies conducted in patients with major mental illnesses are limited in their ability to distinguish potential drug effects from glucose dysregulation intrinsic to the psychiatric disorder.

Melkersson et al. (2001) investigated the in vitro effects of antipsychotic drugs on pancreatic insulin release in isolated rat pancreatic islets. No significant effects on insulin release were observed for any drug during 1 hour of exposure and no significant effect on insulin release was observed for olanzapine, chlorpromazine, perphenazine, zuclopenthixol or risperidone during 4 hours of exposure. Islets incubated with haloperidol for 4 hours released less insulin in response to glucose while basal insulin release from islets incubated with clozapine for 4 hours was significantly greater than controls. Glucose stimulated release by islets incubated with clozapine was not different from controls.

Ardizzone et al, (2001) reported that risperidone and clozapine interact with glucose transporters and inhibit the uptake of glucose into rat PC12 cells. The relevance of these findings to human glucose homeostasis is unclear.

Henderson (2000) assayed glucose and insulin levels after glucose challenge in patients taking neuroleptic drugs. They found no statistically significant differences in glucose effectiveness, but rank ordering on insulin sensitivity was clozapine < olanzapine < risperidone. This study did not include an untreated control group, but historical norms for results of this test appear to fall between results for olanzapine- and risperidone-treated patients.

Newcomer et al, (2002a) compared 31 healthy control subjects with 48 patients with schizophrenia treated with olanzapine (n=12), risperidone (n=10), clozapine (n=9) and conventional antipsychotic drugs (n=17). Significant glucose elevations were observed in olanzapine-treated and clozapine-treated patients compared with patients receiving typical antipsychotic drugs or healthy controls. Risperidone-treated patients had significant elevations in glucose compared with healthy controls but not versus patients receiving typical antipsychotic drugs. There were no differences between patients treated with typical antipsychotic drugs and healthy controls. This study was limited by small sample size, use of non-randomised, open-label, cross-sectional design and the need for extensive statistical modelling to control for confounding factors.

Newcomer et al. (2002b) examined insulin sensitivity in patients treated with antipsychotic drugs using the hyperinsulinemic euglycemic clamp in a more recent study. Insulin sensitivity (as indicated by the dextrose infusion rate) was significantly lower in patients taking risperidone, olanzapine and typical antipsychotic drugs compared with slim controls but not with controls of average weight. There were no statistically significant differences in insulin sensitivity between patients taking risperidone, olanzapine or typical antipsychotic drugs.

5. Clinical trials sponsored by the MAH

The MAH has undertaken two clinical trials (HGIM and S013) to study the potential effect of olanzapine on pancreatic function and insulin sensitivity in comparison to placebo and risperidone. These studies are now described together with data from other two clinical trials comparing olanzapine with placebo (HGHL) and olanzapine with lithium (HGHT) in recurrence prevention in bipolar disorder during which blood glucose and glycosylated haemoglobin (in HGHL only) was evaluated. In addition, an analysis of Integrated Clinical Trial Database has been performed.

5.1 Effect of Antipsychotic Therapy on Glycemic Control: A Comparison of Olanzapine, Risperidone, and Placebo in Healthy Subjects (F1D-MC-HGIM)

This study was designed to determine if atypical antipsychotics have an acute direct effect on pancreatic beta cell function causing decreased insulin secretion in healthy subjects treated with olanzapine 10 mg/day (n=17), in comparison to risperidone 4 mg/day (n=13) or placebo (n=18) for 15 to 17 days. Insulin secretion was quantitatively assessed using the hyperglycemic clamp at baseline and endpoint. Glucose is infused over an extended period of time, and plasma glucose is maintained in a hyperglycaemic range that stimulates insulin secretion. Clamp studies have been very sensitive instruments for detecting impaired capacity to secrete insulin in response to glucose challenge.

Weight increased significantly ($p<.01$) in both the olanzapine (2.8 ± 1.7 kg) and risperidone (3.1 ± 2.1 kg) treatment groups. Fasting insulin levels were also increased significantly ($p<.05$) compared to placebo during treatment with olanzapine (40%) or risperidone (36%). Fasting glucose was not changed in either active treatment group (Table 2).

<u>Table 3.</u> Changes in Weight and Fasting Measures of Glucose and Insulin

Group	Weight (kg)	Glucose (mmole/L)	Insulin (pmole/L)
Olanzapine	2.8 (1.7)a,*	0.02 (0.53)	19.8 (54.6)b,**

Risperidone	3.1 (2.1)a,*	0.14 (0.44)	15.0 (28.2)c
Placebo	0.5 (1.2)	–0.08 (0.31)	–13.8 (17.4)

a p <.001 vs. placebo
b p ≤.02 vs. placebo
c p <.05 vs. placebo
*p <.01 within group
**p≤.04 within group

Using the hyperglycaemic clamp, an increase in the total insulin response to hyperglycaemic challenge was observed after treatment with olanzapine or risperidone. Further, the magnitude of the increase (~25%) in the total insulin response (weighted mean insulin level, 0 to 240 minutes) was similar for the active therapy groups. Further, using linear multivariate regression analysis (with BMI change = 0) to adjust for the impact of weight gain, no significant changes were observed in the olanzapine or risperidone groups for Total Insulin Response, total C peptide response, fasting insulin, or the insulin sensitivity index (M/I) derived from steady-state measures during the hyperglycaemic clamp.

Limitations of this study are similar to those discussed for the euglycemic clamp and include a small number of individuals examined, a relatively short exposure time, and use of healthy volunteers rather than patients with psychiatric illnesses. Results of this study found similar changes in body weight, fasting insulin, and insulin secretion during hyperglycaemia in healthy volunteers treated with olanzapine or risperidone. An increase in total insulin response during the clamp was seen with both drugs and was most likely related to weight gain observed during therapy. Weight related increases in insulin response and decreases in the insulin sensitivity index calculated from steady-state measures during the hyperglycaemic clamp were observed and are consistent with the known effects of weight gain and short-term overfeeding on glucose and insulin homeostasis. However, after accounting for the impact of weight gain in linear regression analyses, results of this study do not suggest that subjects treated with olanzapine or risperidone experienced decreased insulin or C peptide responses during the hyperglycaemic challenge.

In summary, results of this study did not suggest an acute weight-independent effect of olanzapine or risperidone to decrease insulin secretion or insulin sensitivity during a prolonged hyperglycaemic challenge (15 to 17 days of treatment) in healthy subjects.

5.2 Effect of Antipsychotic Therapy on Insulin Sensitivity: A Comparison of Olanzapine, Risperidone, and Placebo in Normal Subjects (F1D-MC-S013)

This was a 3-week, prospective, single-blind study in healthy volunteers to test the hypothesis that olanzapine and risperidone do not have a direct effect on insulin sensitivity that impairs peripheral tissue glucose uptake.

The primary objective of this study was to assess whether olanzapine 10 mg/day had an adverse effect on glucose metabolic parameters in normal, nondiabetic subjects as measured by the insulin sensitivity index, which is the ratio of the glucose infusion rate (M) and steady-state insulin concentration (I) during an euglycemic clamp. Specifically, the primary safety analysis was whether there is a

statistically significant within-group percent change in the quotient of M (glucose disposal rate) divided by I (insulin concentration), as in the following:

$$\frac{(M/I)2-(M/I)1}{(M/I)1} \text{ x } 100$$

The secondary objectives of this study were 1) to assess whether risperidone 4 mg/day or placebo have an adverse effect on glucose metabolic parameters in normal, nondiabetic subjects as measured by changes in the insulin sensitivity index (M/I) during an euglycemic clamp, 2) to assess subjects' baseline-to-endpoint changes in meal tolerance testing via Cmax, Tmax, and area under the curve (AUC) analyses for olanzapine, risperidone, and placebo, 3) to evaluate the baseline-to- endpoint changes in weight for olanzapine, risperidone, and placebo and 4) to assess subjects' baseline-to-endpoint changes in lipid parameters (triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol) for olanzapine, risperidone, and placebo.

55 out of the 64 randomised subjects completed the protocol. Treatment groups were well-matched, except that the risperidone group contained only 14 completing subjects due to study discontinuations with blinded replacement. Following diet stabilization, subjects underwent a baseline mixed meal tolerance (MMT) test and a two-step hyperinsulinemic euglycemic clamp, after which subjects were randomised 1:1:1 to olanzapine (10 mg/day), risperidone (4 mg/day), or placebo. After 21 to 23 days of treatment, an endpoint MMT test and euglycemic clamp were performed. The action of insulin was assessed at 2 insulin infusion rates, 20 mIU/m2/min (low dose) and 120 m1U/ni2/min (high dose). These doses of insulin result in serum insulin concentrations that approximate the ED50 (low dose) and the maximum (high dose) concentration for stimulation of peripheral glucose uptake in nonobese, nondiabetic subjects. Insulin sensitivity was quantitated as M/I, which is the steady-state glucose disposal rate (M) divided by the steady-state mean insulin concentration (I). For the analysis of insulin sensitivity, steady-state at low insulin concentration was defined as the 140- to 160-minute interval of the clamp and as the 260- to 280-minute interval for the high insulin concentration.

No deaths or serious adverse events occurred during this study. One subject in the risperidone group discontinued due to an adverse event (anxiety). No statistically significant differences were observed in the frequency of adverse events between the treatment groups.

Using a two-step euglycemic clamp to quantitate peripheral tissue insulin sensitivity, there were no significant within-group changes (percent change or absolute value) or between-group differences observed for the mean change in insulin sensitivity at low insulin steady-state. There were also no significant changes in the maximal response of peripheral glucose uptake measured at the high insulin steady states. Several small, statistically significant changes in glucose and insulin were observed for the active therapy groups during MMT testing. Given the small magnitude of the observed changes, the clinical significance is uncertain but may be minimal in the absence of evidence of altered insulin sensitivity (Table 4).

Weight increased significantly in both the olanzapine (1.95 kg) and risperidone (1.67 kg) groups compared to placebo. Statistically significant within-group changes (increase) in fasting glucose and insulin were noted in the olanzapine group. The change in fasting insulin was significantly different

from the risperidone group (but not placebo); however, the change in fasting glucose was not significantly different from changes observed in either the placebo or risperidone groups, (Table 5).

Fasting free fatty acids (FFA) decreased significantly in all treatment groups, (Table 5). Statistically significant within-group changes (increase) were observed in total cholesterol for the olanzapine group and in LDL cholesterol for the olanzapine and placebo groups, but these changes were not different between treatment groups. In the olanzapine group, a significant within-group change (increase, 29%) in fasting triglycerides was observed and this change was significant compared placebo. The increase (19%) in fasting triglyceride levels observed for the risperidone group did not achieve statistical significance compared to placebo. Overall changes in fasting triglyceride levels observed in this study were significantly positively correlated with changes in BMI. The clinical significance of the significant decrease in the FFA area under the curve (AUC) in the risperidone group is also uncertain.

Table S013.4.13. Summary of Euglycemic Hyperinsulinemic Clamp Results From Baseline to Endpoint F1D-MC-S013

Low Insulin Phase

Items	Therapy	Baseline N	Baseline Mean	Baseline Std	Change to Endpoint N	Change to Endpoint Mean	Change to Endpoint Std.	Within P-val	Overall Pairwise P-val Pval	Pval Vs.Ris	Pval Vs.Pla
Glucose	Olz10.0	22	95.505	10.327	22	-3.802	10.428	.1020	.1455	.0555	.2511
(mg/dL)	Risp.	14	91.661	3.606	14	1.440	7.614	.4915			.6120
	Placebo	19	91.454	3.343	19	-0.271	4.265	.7649			
Insulin	Olz10.0	22	28.570	5.730	22	0.173	5.927	.8525	.0753	.2696	.1605
(uIU/ml)	Risp.	14	27.668	6.027	14	-2.618	6.273	.1424			.0248
	Placebo	19	26.268	7.008	19	3.268	9.700	.1592			
M	Olz10.0	22	4.841	1.725	22	0.056	2.048	.8999	.1320	.2152	.3319
(mg/kg/min)	Risp.	14	4.884	2.127	14	-0.582	1.199	.0928			.0453
	Placebo	19	4.077	1.436	19	0.476	0.803	.0186			
C-peptide	Olz10.0	22	1.824	0.774	22	0.099	0.809	.5736	.8624	.5883	.8206
(ng/ml)	Risp.	14	1.552	0.832	14	-0.039	0.701	.8370			.7552
	Placebo	19	1.377	0.614	19	0.084	0.483	.4598			
M/I	Olz10.0	22	0.175	0.064	22	4.630	36.092	.5538	.8427	.9266	.6247
& % change	Risp.	14	0.186	0.092	14	3.249	33.739	.7244			.6037
	Placebo	19	0.165	0.076	19	11.351	47.730	.3136			
M/I	Olz10.0	22	0.175	0.064	22	0.005	0.068	.7483	.6832	.8152	.5012
& absolute	Risp.	14	0.186	0.092	14	-0.002	0.064	.9214			.4157
change	Placebo	19	0.166	0.076	19	0.022	0.110	.4022			

Model for Glucose: change(abs.)=therapy+base_bmi
Model for Insulin: change(abs.)=therapy+base_bmi
Model for M: change(abs.)=therapy+base_bmi
Model for C-peptid: change(abs.)=therapy+base_bmi
First model for M/I: change(%)=therapy+base_bmi
The model for Within Pval:change=base_bmi by therapy
The range for Steady State: 140<=Clampref<=160

RMP.F1DS8013.SASPGM(CMPYBE01) RMX0207

Table 4. Euglycaemic Hyperinsulinemic Clamp results from baseline to endpoint in FID-MC-S013.

Table S013.4.13. Summary of Euglycemic Hyperinsulinemic Clamp Results From Baseline to Endpoint F1D-MC-S013 (concluded)

High Insulin Phase

Items	Therapy	N	Baseline Mean	Std	Change to Endpoint N	Mean	Std.	Within P-val	Overall Pval	Pairwise P-val Vs.Ris	Vs.Pla
Glucose	Olz10.0	22	92.058	5.398	22	-0.822	5.015	.4506	.7084	.7704	.4093
(mg/dL)	Risp.	14	92.662	6.611	14	-0.389	6.893	.8359			.6491
	Placebo	19	90.816	3.716	19	1.036	4.746	.3539			
-Insulin	Olz10.0	22	214.379	45.697	22	-10.025	26.554	.0911	.2906	.6298	.1197
(uIU/ml)	Risp.	14	187.014	47.428	14	-4.682	27.184	.5305			.3517
	Placebo	19	208.684	60.803	19	6.237	39.643	.5016			
-M	Olz10.0	22	12.734	2.798	22	-0.019	1.992	.9655	.5158	.2528	.6810
(mg/kg/min)	Risp.	14	13.331	3.944	14	-0.667	1.702	.1664			.4698
	Placebo	19	12.136	2.034	19	-0.287	1.102	.2709			
-C-peptide	Olz10.0	22	1.234	0.582	22	0.335	0.691	.0338	.3532	.1511	.5538
(ng/ml)	Risp.	14	1.103	0.488	14	0.046	0.589	.7727			.3986
	Placebo	19	0.841	0.442	19	0.197	0.430	.0657			
-M/I	Olz10.0	22	0.063	0.024	22	6.891	24.545	.2021	.2753	.3053	.1235
& % change	Risp.	14	0.077	0.026	14	-0.569	21.378	.9086			.6073
	Placebo	19	0.063	0.023	19	-4.656	17.884	.2713			
-M/I	Olz10.0	22	0.063	0.024	22	0.004	0.021	.4342	.3579	.2405	.2216
& absolute	Risp.	14	0.077	0.026	14	-0.003	0.017	.4972			.9768
change	Placebo	19	0.063	0.023	19	-0.004	0.010	.1249			

-Model for Glucose: change(abs.)=therapy+base_bmi
Model for Insulin: change(abs.)=therapy+base_bmi
Model for M: change(abs.)=therapy+base_bmi
Model for C-peptid: change(abs.)=therapy+base_bmi
First model for M/I: change(%)=therapy+base_bmi
The model for Within Pval:change=base_bmi by therapy
The range for Steady State: 260<=Clamprof<=280

RMP.F1DSS013.SASPGM(CMPYBE01) RMX0207

Table 4. Cont'd

Table S013.4.6. Analysis of Difference in Mean Fasting Blood Glucose, Mean Fasting Insulin, Mean Fasting C-Peptide, and Mean Fasting Free Fatty Acid Concentrations Before and After Treatment
F1D-MC-S013

Fasting Measurements

Items	Therapy	N	Baseline Mean	Std	N	Change to Endpoint Mean	Std	Within Pval	Overall Pval	Pairwise Pval Vs. Risp	Vs. Pla.
Fasting Glucose(mg/dL)	Olz10.0	22	86.364	4.658	22	2.318	4.423	.0227	.2166	.0957	.2383
	Risp.	14	91.357	6.732	14	-0.750	6.739	.6839			.5603
	Placebo	19	87.211	6.246	19	0.342	5.020	.7698			
Fasting C-peptid(ng/ml)	Olz10.0	22	1.668	0.411	22	0.336	0.441	.0018	.0003	.0001	.0218
	Risp.	14	2.081	0.804	14	-0.250	0.454	.0599			.0393
	Placebo	19	1.611	0.431	19	0.044	0.271	.4912			
Fasting Insulin(uIU/ml)	Olz10.0	22	6.052	2.117	22	2.755	4.450	.0085	.0924	.0386	.7891
	Risp.	14	10.525	4.715	14	-0.618	3.799	.5533			.0744
	Placebo	19	7.092	2.768	19	2.363	5.377	.0714			
Fasting Free fat(mEq/L)	Olz10.0	22	0.480	0.165	22	-0.107	0.217	.0310	.7642	.4704	.8348
	Risp.	14	0.536	0.195	14	-0.161	0.210	.0132			.6057
	Placebo	19	0.555	0.237	19	-0.121	0.222	.0287			

Table 5. Mean fasting blood glucose, insulin, C-peptide and FFA concentrations in FID-MC-S013.

The MAH concludes that olanzapine and risperidone had no significant effect on the insulin sensitivity of peripheral tissue glucose uptake in healthy volunteers. These data are in line with those of Newcomer et al. (2002) who found no significant difference in glucose disposal rates among matched groups of overweight patients with schizophrenia treated with olanzapine, risperidone or typical antipsychotic drugs using the same methodology.

5.3 Analysis of Integrated Clinical Trial Database

Allison and colleagues conducted a retrospective analysis of pooled data from the olanzapine-integrated database (data on file), which included double-blind, randomised, direct-comparator-controlled olanzapine clinical trials of schizophrenia-spectrum disorders.

These analyses compared the mean change in random plasma glucose, which was measured periodically during head-to-head clinical trials of olanzapine in patients with schizophrenia over an observation period of 18 to 52 weeks. Mean random glucose increases of 0.8 to 4.6 mg/dL were observed in olanzapine-treated patients. This increase was significantly more than that observed with haloperidol or placebo, not significantly different from that seen with risperidone, and significantly less than observed with clozapine. These analyses controlled for a number of factors, including age, time of exposure to antipsychotic therapy, baseline BMI, baseline glucose, and change in BMI during treatment (Table 3.3).

Table 6. Mean* change in baseline to endpoint random blood glucose concentrations

Database	**Mean change ± S.E. (mg/dL)**		**p-value**
	Olanzapine	**Comparator**	
Haloperidol-controlled	4.56 ± 0.57	0.22 ± 0.93	0.0001
Risperidone-controlled	4.51 ±1.79	2.58 ± 1.12	0.0626
Clozapine-controlled	3.17 ± 1.36	13.22 ± 2.19	0.0001
Placebo-controlled	0.77 ± 1.12	-1.28 ± 1.5	0.0035

*Mean refers to least-squares mean.

Treatment-emergent glycemic changes were most pronounced in patients treated with clozapine, as indicated by a significantly greater mean glucose increase. Although greater than what was observed with haloperidol or placebo, increases in glucose during treatment with olanzapine were relatively small in magnitude across all databases, and were not significantly different from the mean glucose increase observed during treatment with risperidone.

6. New Clinical Trial Data

Data on glycaemic control in patients treated with olanzapine, active comparators and placebo have been provided to the EMEA in the MAH's dossiers submitted to date. The MAH has submitted similar data from clinical trials HGHL and HGHT with the application for a new olanzapine claim for bipolar recurrence prevention (See the Rapporteur's Assessment Report).

A preliminary data from trials HGHL and HGHT are briefly reviewed also here as follows:

6.1 HGHL

Design: A twelve-month double blind randomised comparison of olanzapine versus placebo in the recurrence prevention in patients with bipolar disorder who had been stabilised with olanzapine during the 6-12 week open label acute treatment phase.

Results: Mean non-fasting glucose levels did not change significantly from base line to end point during the trial and did not differ significantly between olanzapine and placebo cohorts at base line or end point. There were no significant differences within either cohorts or between the two cohorts for high treatment emergent blood non-fasting glucose levels.

Glycosylated haemoglobin (HbA1c) above 6.1% in patients who had values ≤6.1% at baseline were regarded as suggestive of potential diabetes mellitus. 31 out of the 486 patients (6.4%) during the open-label acute period had treatment-emergent HbA1c >6.1%. 4 of 129 olanzapine-treated patients (3.1%) and 0 of 93 placebo-treated patients had treatment-emergent HbA1c >6.1% during the 12 month double-blind period (p=0.141). None of the treatment-emergent abnormal values for HbA1c in non-diabetic patients exceeded 6.8%. Most patients with treatment-emergent HbA1c >6.1% possessed numerous baseline risk factors for impaired glycaemic control, used concomitant medications or illicit substances associated with impaired glycaemic control or experienced treatment emergent weight gain.

3 out of the 35 patients had pre-existing diabetes mellitus at baseline as evidenced by the presence of secondary conditions corresponding to MedDRA terms for diabetes at enrolment. All 3 patients developed treatment emergent weight gain in association with changes in their HbA1c values. The mean HbA1c at baseline was 5.9% (range 5.2% - 6.1%) in the 32 patients with treatment-emergent HbA1c >6.1% who did not have diabetes at baseline. The mean HbA1c was 5.4% for those 453 non-diabetic patients who did not have treatment-emergent HbA1c above 6.1%.

6.2 HGHT

Design: A twelve-month double blind randomised comparison of olanzapine versus lithium in recurrence prevention of patients with bipolar disorder who had been stabilised with olanzapine and lithium during the 6-12 week open label acute treatment phase.
Results: Mean non- fasting glucose levels did not change significantly from base line to end point during the trial and did not differ significantly between olanzapine and lithium cohorts at base line or end point. There were no significant differences within either cohort. Glycosylated haemoglobin (HbA1c) was not evaluated in this clinical trial.

Conclusions of the MAH: The pattern and incidence of hyperglycemia in these two studies is very similar to that seen in previously reported olanzapine studies and is consistent with the data currently provided in the SPC. It therefore seems reasonable to conclude from clinical trials HGHL and HGHT that olanzapine does not differ significantly from lithium or placebo in its effect on mean non-fasting blood glucose or glycosylated haemoglobin (HbA1c) in patients with bipolar disorder treated for twelve months.

Assessor's conclusions: *As the data currently referred to in the SmPC and reviewed previously by the CPMP is concentrating on clinical trial population with schizophrenia, it is interesting to review more closely the results in the population of patients with bipolar disorder. The MAH has analysed random*

non-fasting glucose and GHbA1c in the long-term comparative studies included in the currently ongoing type II variation to extend the indications to relepse prevention in bipolar disorder. Details of the study designs and patient populations can be found in the Rapporteur's draft variation assessment report dated 7 January 2003. The results are briefly desctibed below.

Changes in nonfasting glucose measurements were examined across the various study databases. The analyses performed included assessment of mean change from baseline to to endpoint and incidence of high nonfasting glucose at any time and at endpoint.

As shown in Table WS.3.49, mean changes in nonfasting glucose were small across all databases, with just one statistically significant treatment group difference. However, in the overall database, the increase from baseline to endpoint was statistically significant. This is a known effect of olanzapine from previous clinical trial database analyses and is included in the current SmPC.

Table WS.3.49. Nonfasting Glucose (mmol/L)
Mean Change from Baseline to Endpoint
Summary Across Databases

			Baseline		Change to endpoint		
Database	Therapy	N	Mean	SD	Mean	SD	p-Value[a]
HGHL	Olanzapine	216	5.92	3.00	0.22	1.89	.353
	Placebo	128	5.84	2.73	0.01	1.94	
HGHT	Olanzapine	207	5.60	1.16	0.26	1.51	.159
	Lithium	206	5.81	1.58	0.13	1.57	
HGHQ	Olanzapine	119	5.98	2.78	0.03	1.80	.222
	Divalproex	116	5.61	2.21	-0.15	1.59	
HGFU	Olanzapine+MS	61	6.12	2.94	0.41	2.68	.039
	Placebo+MS	52	5.69	1.66	-0.34	1.23	
OID	Olanzapine	1399	5.58	1.77	0.22	1.88	<.001

Abbreviations: MS = mood stabilizer (lithium or valproate); N = number of patients in each group having the variable in both baseline and postbaseline visits; OID = overall integrated database; SD = standard deviation.

--

Further analyses of the proportions of patients with high nonfasting glucose were performed using two different definitions for " high." One analysis (" HIGH1") assessed the incidence of patients with values of at least 11.1 mmol/L among patients with values less than 11.1 mmol/L at baseline. A single random glucose value of 11.1 mmol/L was chosen as a glucose threshold suggestive of diabetes. The current ADA guidelines for the diagnosis of diabetes on the basis of random glucose require a second confirmatory random glucose measurement of at least 11.1 mmol/L with demonstration of diabetic symptoms before a definitive diagnosis of diabetes is made.

A plasma glucose value between 7.8 and 11.1 mmol/L in an oral glucose tolerance test is considered evidence of impaired glucose tolerance (ADA 2002). A second analysis (" HIGH2") assessed the

incidence of patients with postbaseline nonfasting glucose values of at least 11.1 mmol/L among patients without preexisting diabetes and with nonfasting glucose values less than 7.8 mmol/L at baseline.

Table WS.3.50. Incidence of Treatment-Emergent High Nonfasting Blood Glucose Values
Summary Across Databases

		At Any Time					At Endpoint				
Event[a]	Dbase	Ther	N	n	%	p	Ther	N	n	%	p
HIGH1	HGHL	olz	206	3	1.5%	1.000	olz	206	3	1.5%	1.000
		pla	122	2	1.6%		pla	122	1	0.8%	
	HGHT	olz	206	8	3.9%	.106	olz	206	5	2.4%	.216
		lith	198	2	1.0%		lith	198	1	0.5%	
	HGHQ	olz	113	6	5.3%	.280	olz	113	0	0.0%	1.000
		dvpx	113	2	1.8%		dvpx	113	1	0.9%	
	HGFU	olz+MS	55	1	1.8%	1.000	olz+MS	55	0	0.0%	-
		pla+MS	49	0	0.0%		pla+MS	49	0	0.0%	
	OID	olz	1362	34	2.5%	na	olz	1362	17	1.2%	na
HIGH2	HGHL	olz	190	1	0.5%	1.000	olz	190	1	0.5%	1.000
		pla	108	1	0.9%		pla	108	0	0.0%	
	HGHT	olz	163	0	0.0%	.494	olz	163	0	0.0%	.494
		lith	159	1	0.6%		lith	159	1	0.6%	
	HGHQ	olz	104	3	2.9%	.246	olz	104	0	0.0%	-
		dvpx	101	0	0.0%		dvpx	101	0	0.0%	
	HGFU	olz+MS	50	0	0.0%	-	olz+MS	50	0	0.0%	-
		pla+MS	47	0	0.0%		pla+MS	47	0	0.0%	
	OID	olz	1238	12	1.0%	na	olz	1238	6	0.5%	na

Abbreviations: Dbase = database; dvpx = divalproex; lith = lithium; MS = mood stabilizer (lithium or valproate); N = number of patients with baseline within required range; n = number of patients meeting the criterion postbaseline; na = not applicable; OID = overall integrated database; olz = olanzapine; p = p-value from a two-tailed Fisher's exact test; pla = placebo; Ther = therapy .

[a] HIGH1 = <11.1 mmol/L at baseline and ≥11.1 mmol/L; HIGH2= ≤7.8 mmol/L at baseline and ≥11.1 mmol/L in patients who did not have diabetes at baseline.

--

To better characterize patients with treatment-emergent HIGH1 glucose abnormalities (11.1 mmol/L if <11.1 mmol/L at baseline), a listing of these patients showing basic demographic information and risk factors for diabetes was prepared. Risk factors that were considered included age ≥45, body mass index (BMI) ≥25, non-Caucasian origin, and presence of hypertension at baseline. Numerous diabetes risk factors were not considered in this listing as the data were not collected.

*Of the 34 patients with treatment-emergent **HIGH1 glucose**, all had at least one risk factor for diabetes at baseline: 1 patient had four risk factors, 11 patients had three risk factors, 15 patients had two risk factors, and 7 patients had one risk factor. All but 2 of the patients gained weight during*

treatment, with 15 gaining 5 kg or more. Six of the 34 patients had preexisting diabetes at baseline. Interpretation of high nonfasting glucose values in this population is confounded by the underlying diabetes. An additional 16 patients had baseline nonfasting glucose ≥7.8 mmol/L, suggesting abnormal glycemic control at baseline. Five of the 16 patients had three risk factors, 6 patients had two risk factors, and 5 patients had one risk factor.

The 12 remaining patients met the ***HIGH2 criteria*** *for glucose abnormality (were not known to have diabetes at baseline, had baseline nonfasting glucose <7.8 mmol/L, and had treatment-emergent nonfasting glucose ≥11.1 mmol/L). Of these 12, four were taking concomitant medications associated with increased risk for glucose dysregulation. One patient had all four of the assessed risk factors, 4 patients had three risk factors, 6 patients had two risk factors, and 1 patient had one risk factor.*

Overall, nonfasting glucose results seen across all the studied databases are consistent with what has been observed in previous olanzapine studies and the current European SPC. Olanzapine use is associated with increases in non-fasting glucose especially in patients with pre-existing diabetes or risk factors for diabetes. The incidence of treatment-emergent nonfasting glucose ≥11.1 mmol/L with baseline <11.1 mmol/L at any time in olanzapine-treated patients in the overall integrated database was 2.5%. When patients who had preexisting diabetes or who had abnormal glycemic control at baseline were excluded from the analysis, the incidence was 1.0%.

HbA1c data were only collected in Study HGHL and were examined as part of the HGHL clinical study report database and as part of the overall integrated database. The analyses performed included assessment of mean change from baseline to endpoint (Table WS.3.52).

Table WS.3.52. Glycosylated Hemoglobin (HbA1c) Mean Change from Baseline to Endpoint HGHL

			Baseline		Change to endpoint		
Dataset	Therapy	N	Mean	SD	Mean	SD	p-Value[a]
HGHL OL	Olanzapine	558	5.7%	0.8%	0.1%	0.4%	<.001
HGHL DB	Olanzapine	170	5.8%	1.3%	0.05%	0.4%	.060
	Placebo	111	5.7%	1.0%	-0.05%	0.4%	

Abbreviations: HGHL DB = double-blind period of Study HGHL; HGHL OL = acute open-label treatment period of Study HGHL; N = number of patients with a normal baseline and at least one postbaseline assessment; SD = standard deviation.

[a] Within-group p-value for HGHL OL calculated with Student's t-test; treatment group differences for HGHL DB calculated with ANOVA.

--

Although the mean chance in glycated Hb is not clinically significant, the results are well in line with an impact of olanzapine treatment on glycaemic control. In the overall integrated database, 35 of 488 patients (7.2%) had treatment-emergent increased HbA1c >6.1%. Among the 468 patients who were normoglycemic at baseline (HbA1c ≤6.1%, nonfasting glucose <7.8 mmol/L, and no secondary conditions indicative of glucose dysregulation), 25 (5.3%) had treatment-emergent HbA1c >6.1%. As a

group, these 25 patients had numerous risk factors for diabetes, all but one gained weight while taking olanzapine, and 13 were taking concomitant medications associated with increased risk of glucose dysregulation. In the placebo-controlled trial, the incidence of increased HbA1c was 0.0% in the placebo group and 3.1% in the olanzapine group.

In the context of these findings, the MAH has not analysed the impact of change in body weight during treatment on non-fasting glucose. Elevated glucose levels are mentioned in Section 4.8 among common (1-10%) undesirable effects and warnings have been included in Section 4.4.

The rapporteur disagrees with the MAH's conclusion and considers that the data do suggest a causal relationship between worsening glycaemic control and olanzapine treatment. The bipolar patient database analysis suggests, in line with the current SmPC that the risk is mostly confined to patients who have pre-existing abnormalities in glycaemic control or risk factors for the development of diabetes mellitus. A likely explanation is body weight gain.

7. Impact of SmPC Changes on Reporting Rates of Glucose-related Adverse Events

The CPMP and PhVWP upon completing their September 2002 meeting requested that the olanzapine MAH evaluate the impact of the SPC changes regarding glucose-related adverse events on reporting of serious outcomes. The primary purpose of this review is to generate and compare reporting ratios for glucose-related adverse events before and after the July 1999 glucose-related adverse events changes in the SPC.

The changes introduced in the SPC and their timing has been described in Table 1 of this AR (page 1).

This review compares reporting rates of diabetic ketoacidosis (DKA), nonketotic hyperglycemic-hyperosmolar coma (NHHC) and clinically non-serious glucose-related adverse events before and after the olanzapine related SPC label changes of July 1999. Data were collected and reviewed for the 15 EU countries.

Comparisons between similar glucose-related adverse events are made with the use of reporting ratios and proportional reporting ratios (PRR). A reporting ratio is the number of adverse event(s) reports of interest for a designated time period divided by all adverse event reports for the same drug during the same time period. Reporting ratios for the event(s) of interest but different time periods can then be compared with a PRR. This simply entails dividing an event's reporting ratio from one time period by that of another. For the purpose of this review a PRR of 2 or more was considered significant.

Data was collected and compared from the 1-year period of time before and after the SPC label change as well as an extended period of time after the July 1999 label change. Time period 1 encompasses July 1,1998 to June 30, 1999. Time period 2 encompasses July 1, 1999 to June 30, 2000 and time period 3 encompasses October 1st, 2001 to September 30th, 2002.

In an effort to detect any effect of the SPC label change, similar glucose-related adverse events MedDRA preferred terms utilized during periods 1, 2 and 3 were grouped together. In the Results section these groupings are defined for Diabetic Ketoacidosis (Table 1), Nonketotic Hyperglycemic-Hyperosmolar Coma (Table 2) and clinically non-serious glucose-related adverse events (Table 3). The

tables also provide the absolute numbers of events coded to the individual preferred terms during periods 1,2 and 3.

Table 1.
MedDRA Preferred Terms Representative of Diabetic Ketoacidosis and Utilized in the MAH's Adverse Event Database During Periods 1, 2 and 3

MedDRA Preferred Terms	Period 1	Period 2	Period 3
Diabetic Ketoacidosis	2	0	9
Ketoacidosis	1	1	5
Metabolic Acidosis Nos	1	1	0
Total	**4**	**2**	**14**

Table 2.
MedDRA Preferred Terms Representative of Nonketotic Hyperglycemic-Hyperosmolar Coma and Utilized in the MAH's Adverse Event Database During Periods 1, 2 and 3

MedDRA Preferred Term	Period 1	Period 2	Period 3
Diabetic Coma Nos	1	1	3
Diabetic Hyperglycaemic coma	0	0	2
Total	**1**	**1**	**5**

Table 3.
MedDRA Preferred Terms Representative of Clinically Non-Serious Glucose-Related Adverse Events and Utilized in the MAH's Adverse Event Database During Periods 1, 2 and 3

MedDRA Preferred Term	Period 1	Period 2	Period 3
Blood Glucose Abnormal			1
Blood Glucose Increased	5	2	19
Diabetes Mellitus Aggravated	0	2	14
Diabetes Mellitus Inadequate Control	2	3	7
Hyperglycaemia Nos	9	19	64
Diabetes Mellitus Insulin Dependent	1	0	7
Diabetes Mellitus Non-insulin Dependent	1	3	19
Diabetes Mellitus NOS	4	15	56
Glycosylated Haemoglobin	0	0	1

Increased			
Gestational Diabetes	0	0	4
Insulin Requiring Type 2 Diabetes Mellitus	0	1	0
Total	**22**	**45**	**183**

Table 4.

Glucose-Related Adverse Events and Reporting Ratios for Olanzapine

	Reporting Ratio (%)		
Glucose-Related Adverse Events	**Period 1**	**Period 2**	**Period 3**
Events representative of DKA	**0.28**	**0.16**	**0.46**
Events representative of NHHC	**0.07**	**0.08**	**0.16**
Events representative of DKA and NHHC	**0.35**	**0.24**	**0.62**
Events representative of non-serious glucose-related adverse events	**1.52**	**3.56**	**5.95**

*Total of all reported adverse events for olanzapine period 1, 1445.
Total of all reported adverse events for olanzapine period 2, 1265.
Total of all reported adverse events for olanzapine period 3, 3075.

Proportional Reporting Ratios for Olanzapine and Glucose-Related Adverse Events For Periods 1 and 2

Events representative of DKA; reporting ratio period 2 / reporting ratio period 1:
0.16 / 0.28 = 0.57

Events representative of NHHC; reporting ratio period 2 / reporting ratio period 1:
0.08 / 0.07 = 1.14

Events representative of non-serious glucose-related adverse events; reporting ratio period 2 / reporting ratio period 1:
3.56 / 1.52 = 2.34

Proportional Reporting Ratios for Olanzapine and Glucose-Related Adverse Events For Periods 1 and 3

Events representative of DKA; reporting ratio period 3 / reporting ratio period 1:
0.46 / 0.28 = 1.64

Events representative of NHHC; reporting ratio period 3 / reporting ratio period 1:
0.16 / 0.07 = 2.29

Events representative of non-serious glucose-related adverse; reporting ratio period 3 / reporting ratio period 1:
5.95 / 1.52 = 3.91

Results appear to be contradictory when comparing period 1 and 2 PRR values for the clinically serious (DKA and NHHC) glucose-related adverse events and the clinically non-serious glucose-related adverse events. A PRR of 2.34 is felt to represent a significant increase in reporting for clinically non-serious glucose-related adverse events in contrast to the clinically serious events with PRR values of 1 or less.

The MAH considers that there are may be several explanations for this discrepancy. One is technical and involves the MAH's recoding of adverse events from COSTART to MedDRA terminology. A second possibility may be due to the fact that there is only a small number of clinically serious glucose-related adverse events. In the clinical setting, non-serious glucose-related adverse events occur more frequently than serious ones. As a result, an individual prescriber has a much greater chance of detecting and reporting a non-serious event compared to a serious one. If the data are limited then a trend towards increased reporting may first be detected with those events occurring more frequently. Those events occurring less frequently may also tend to be subject to increased reporting after greater patient-time exposure.

This is demonstrated when comparing period 1 and 3 PRR values for the clinically serious (DKA and NHHC) glucose-related adverse events and the clinically non-serious glucose-related adverse events. In contrast to period 1 and 2 PRR values, all values approach or exceed a PRR of 2. Based upon the total number of adverse events (3075) reported in temporal association with olanzapine during period 3 as compared to period 1 (1445), it is estimated that patient exposures may have doubled in period 3.

Over two years have elapsed since the initial July 1999 glucose-related adverse events SPC label changes. During this period of time a general increase in awareness regarding hyperglycemia, schizophrenia and atypical antipsychotics developed and the SPC underwent additional changes in December of 2000 as well as June 2001. Three possible causes of reporting bias that may have impacted the PRRs are:

- The above reference to the SPC changes
- Reports in the medical literature; at scientific conferences; and in the media of glucose-related adverse events temporally associated during treatment with antipsychotics
- An increasing competitive marketplace regarding these issues

The MAH feels that the data is representative of stimulated spontaneous adverse event reporting in both periods 2 and 3. The July 1999 SPC changes may be among the stimulus for increased reporting during period 2. This is most evident with those events reported frequently.

Assessor's comment: The assessor agrees that the metabolic consequences of neuroleptic treatment, especially with atypical neuroleptics, has received considerable coverage in scientific literature, and that increase in awareness may have lead to stimulated reporting for olanzapine after the SmPC

changes in 1999. This situation might be shared by other atypical neuroleptics, but unfortunately proportional reporting ratios are not available for comparison. Time period 2 encompasses a relatively short period after the introduction of SmPC changes and it is therefore not unexpected that only the proportional reporting rate for non-serious reactions, which are the most frequent, increased to a significant extent from time period 1 (i.e. before SmPC changes). The Rapporteur considers that the findings altogether are not unexpected.

8. The Overall Conclusions of the MAH:

- People with major mental illnesses such as schizophrenia or bipolar disorder were regarded as having a higher risk for diabetes mellitus than the general population before antipsychotic drugs were introduced in the 1950's
- People taking typical and atypical antipsychotic drugs for the treatment of these major mental illnesses have a higher risk for diabetes mellitus than the general population
- People taking atypical antipsychotic drugs may have a higher risk for diabetes mellitus than people taking typical antipsychotic drugs
- Data do not appear sufficient to support any conclusions regarding differences in the incidence of diabetes mellitus between patients treated with specific atypical antipsychotic medications
- The review of olanzapine reported glucose-related adverse events and their relationship to SPC changes supports the concept of stimulated reporting. This review demonstrates that SPC labelling, among other things, may have an impact on an individual prescriber's reporting behaviour in the EU countries.

The current European SmPC for olanzapine provides substantial advice on the risk of hyperglycaemia or exacerbation of pre-existing diabetes mellitus in sections 4.4 and 4.8. Based on data from the general and olanzapine specific literature, from the olanzapine clinical trial database, from the Clintrace (Lilly) and MedWatch (FDA) databases and from the clinical experience available from the use of olanzapine in > 10 million patients over the 6 years since it became available in 1996, there appears to be no compelling reason to change the olanzapine SmPC with respect to advice on the risk of hyperglycaemia or exacerbation of pre-existing diabetes mellitus at this time.

9. Overall Conclusion of the Rapporteur

Pathophysiological investigations have not given the answers to the question on the role of olanzapine in the development of diabetes mellitus. The clinical trials using either hyperglycaemic or euglycaemic clamp have been of short duration. Moreover, the subjects in these studies have been healthy volunteers. The pathophysiological processes leading to clinical diabetes take substantial time in many cases. Therefore, short-term trials (clinical or observational cohort studies) are unlikely to provide conclusive evidence of the role of a drug in the development or exacerbation of diabetes in genetically or otherwise susceptible patients.

The MAH has analysed the impact of the SPC changes to reporting rates and proportional reporting rates of glucose-related ADRs. The Rapporteur agrees that the increased reporting rates of ADRs after introduction of warnings in the SmPC are mostly focused on non-serious cases, and that a likely explanation is hightened awareness and subsequent stimulated reporting. The Rapporteur does not

consider that the increased proportional reporting rate of glucose-related ADRs per se warrants further changes in the SmPC.

The epidemiological studies published to date and the database analyses conducted by the MAH suggest that both typical and atypical antipsychotic use is associated with a higher risk for diabetes mellitus compared to the general population/patients not taking antipsychotics.

Patients receiving atypical antipsychotic drugs, including olanzapine, appear to have a higher risk for diabetes mellitus than patients taking typical antipsychotics.

The data do not conclusively demonstrate differences in the risk of diabetes mellitus among atypical neuroleptics. However, spontaneous reporting rates and epidemiological data suggest that olanzapine is not consistently associated with the highest risk among atypical neuroleptics.

As regards olanzapine, short-term mechanistic studies using euglycaemic and hyperglycaemic clamp techniques in healthy volunteers do not suggest that olanzapine is associated with impaired insulin secretion in response to hyperglycaemia or to clinically significant insulin resistance. Both olanzapine and risperidone have been shown to actually increase insulin secretion is response to hyperglycaemia, but the effect is very likely accounted for by body weight increase.

In contrast to the MAH's conclusion, the Rapporteur considers that clinical trials suggest a higher risk of worsening glycaemic control in patients receiving olanzapine compared to non-neuroleptic drugs (lithium and valproate), haloperidol and placebo. The bipolar patient database analysis suggests, in line with the current SmPC, that the risk is mostly confined to patients who have pre-existing abnormalities in glycaemic control or risk factors for the development of diabetes mellitus. A likely explanation is body weight gain.

Spontaneous ADR reporting also suggests that the use of olanzapine and other atypical neuroleptics is associated with glucose dysregulation. The reporting rates for all ADRs pertaining to glucose dysregulation are similar for olanzapine, clozapine, quetiapine and ziprasidone according to FDA MedWatch database. However, the CPMP considers that based on the following findings, a further changes in the information included in SmPC Sections 4.4 and 4.8 are necessary to highlight that diabetes has also been reported in patients who had no known risk factors for diabetes:

→ In some cases, patients had no personal history of diabetes mellitus or hyperglycemia. Indeed :

- *According to the published Medwatch data on reports of olanzapine associated diabetes mellitus (Koller et al), 188 of the 237 cases were newly diagnosed hyperglycemia (79%) including 153 which fit criteria for the diagnosis of diabetes ; 15 cases were fatal, including 14 with newly diagnosed diabetes;*
- *a retrospective analysis of a state hospital's records from July 1992 to May 1999 for development of diabetes mellitus on atypical antipsychotics (Singer et al) showed that of the 34 patients who received atypical APs, 11 had diabetes mellitus onset while taking the atypical drug ;*
- *a retrospective chart review performed by Wilson et al. showed that the overall rate of diabetes mellitus among patients treated with olanzapine (N=2542) was 10.9% with 5% being new onset.*

→ The company has performed an analysis of treatment emergent diabetes (TED) in Lilly integrated clinical trials database. From a large (n=5013) non-diabetic cohort of patients with schizophrenia, 94 patients were identified with TED and 282 patients were identified as possessing uncertain glucose tolerance (UGT). According to figure 2.9 of the Briefing Document on Olanzapine and Glucose Homeostasis, 10% of TED patients and 25% of UGT patients possessed no risk factors for diabetes.

The CPMP considers that prescribers should be informed that diabetes or hyperglycemia have been reported in patients receiving olanzapine, who had no risk factors for diabetes.

Therefore, the following modifications for olanzapine SPC are requested :

Current SPC	**Proposed revised SPC**
Section 4.4 : Hyperglycemia or exacerbation of pre-existing 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 in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	**Section 4.4** : Hyperglycemia <u>and/or development</u> or exacerbation of diabetes mellitus occasionally associated with ketoacidosis or coma, sometimes fatal, have been reported very rarely. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. <u>Although most patients had risk factors for diabetes, hyperglycemia or diabetes mellitus has also been found in patients with no identified risk factors.</u> Appropriate clinical monitoring is advisable <u>particularly</u> in diabetic patients and in patients with risk factors for the development of diabetes mellitus. (see section 4.8 Undesirable Effects).
Section 4.8 : • **Clinical trials** : Metabolism and nutrition disorders : *Common* : Elevated glucose levels In clinical trials with olanzapine in over 5000 patients with baseline 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	**Section 4.8 :** • **Clinical trials** : Metabolism and nutrition disorders : *Common* : Elevated glucose levels In clinical trials with olanzapine in over 5000 patients with baseline 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 hyperglycemia) was 2.0% compared to 1.6% with placebo. Hyperglycemia is also reported as a Very rare (<0.01%) spontaneous event. • **Post-marketing spontaneous reports** : Metabolism and nutrition disorders : *Very rare (<0.01%) :* Hyperglycemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases	glucose levels > 8.9 mmol/l but <11 mmol/l (suggestive of hyperglycemia) was 2.0% compared to 1.6% with placebo. Hyperglycemia is also reported as a Very rare (<0.01%) spontaneous event. • **Post-marketing spontaneous reports** : Metabolism and nutrition disorders : *Very rare (<0.01%) :* Hyperglycemia and/or development or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma, sometimes fatal, have been reported in patients on olanzapine therapy. (see section 4.4 Special Warning and Special Precaution for Use).

10. Recommendation

The review of submitted data does not change the overall benefit-risk profile of olanzapine in the approved therapeutic indications. However, the MAH is asked to revise the information in Sections 4.4 and 4.8 of the SmPC to highlight that hyperglycaemia/diabetes mellitus has also been reported in patients without known risk factors.

There is an ongoing type II variation to extend the indications to relapse prevention in bipolar I disorder. In that context, the Rapporteur recommends that the high frequency of clinically significant weight gain, also an obvious risk for diabetes mellitus, is re-emphasised in SmPC section 4.8 with modifications (see Rapporteur's Assessment Report dated 7 January 2003). It is recommended that the changes outlined above are implemented in the context of these ongoing variations.