

2. WORLDWIDE MARKET AUTHORISATION STATUS

Olanzapine was first approved on 27 September 1996 in the European Union and as of 30 September 2002 has been approved in approximately 107 countries (see Appendix 1).

3. UPDATE ON REGULATORY OR MARKETING AUTHORISATION HOLDER ACTIONS TAKEN FOR SAFETY REASONS

During the period covered by this report (1 April 2002 to 30 September 2002), the major regulatory actions taken for safety reasons are summarised below.

EUROPEAN UNION

Changes to SPC:

- Following a positive opinion by CPMP, the Commission Decision for the type II variation filed for the additional indication “Olanzapine is indicated for the treatment of a moderate to severe manic episode. Olanzapine has not been demonstrated to prevent recurrence of manic or depressive episodes” and corresponding safety advice was received 4 June 2002. The type II variation was for the oral presentations of Zyprexa and Olansek Coated tablets.
- Following PSUR 7 and 8, the CPMP asked the company to amend the SmPCs to include further safety information. Type II variations were filed for Zyprexa Coated Tablets, Zyprexa Powder for Injection, Olansek Coated Tablets and Zyprexa Velotab Orodispersible Tablets in February 2002 to address these points. The proposed changes partly result from the CPMP assessment of the seventh Periodic Safety Update Report, (included in the renewal) and part of the changes are based on the Lilly sponsored studies in psychosis associated with Parkinson’s disease (safety update). In addition, comments made by the PIQ group were addressed. The CPMP opinion and the Commission Decision for these variations were received 31 May 2002 and 9 September 2002 respectively. (see Appendix 2 for details of the changes to the SmPC).
- Following the approval of the manic episode indication for the oral presentations, a type II variation was filed in May 2002 for the Zyprexa 10 mg Powder and Solvent for Solution for Injection and Zyprexa 10 mg Powder for Solution for Injection presentations to add this indication and corresponding safety advice to the SmPC. The positive CPMP Opinion was received 25 July 2002. The Commission Decision is awaited.

AUSTRALIA

Following the mandate, by the Japanese Ministry of Health, Labour and Welfare (MHLW) to expand the olanzapine label regarding hyperglycaemia and diabetes, Lilly advised the Australian Therapeutic Goods Administration (TGA) of this request. The Japanese MHLW mandate was detailed in PRUR 9, Appendix 2.

The TGA consequently requested a change to the olanzapine label as follows:

New Precaution :

There is an increased prevalence of diabetes in patients with schizophrenia. As with some other antipsychotics, exacerbation of pre-existing diabetes has been reported very rarely. Hyperglycaemia, diabetic coma and diabetic ketoacidosis have been reported in very rare cases, sometimes in patients with no reported history of hyperglycaemia (see ADVERSE REACTIONS). Appropriate clinical monitoring is advisable in diabetic patients.

New Adverse Reaction:

Metabolic - Very rare (< 0.01%): exacerbation of pre-existing diabetes

A 'Dear Doctor' letter (copy attached – Attachment 1) was sent out regarding these changes to the label.

NEW ZEALAND

The New Zealand Ministry of Health (MoH) has requested that the sponsors of atypical antipsychotics (Olanzapine, Clozapine, Risperidone and Quetapine) update their data sheet with respect to diabetes related events.

Lilly are currently in the process of addressing this request and will report on its outcome in the next PSUR.

UNITED STATES

No safety-related changes to the Zyprexa labeling occurred during the reporting period.

On October 2, 2002, the MAH proactively submitted data to FDA regarding atypical antipsychotics and glucose metabolism/dysregulation in support of a meeting requested by the MAH. These data included results from Study S013 (Effect of Antipsychotic Therapy on Insulin Sensitivity: A Comparison of Olanzapine, Risperidone, and Placebo in Normal Subjects), analysis of treatment-emergent diabetes in Lilly integrated clinical trial database, analysis of postmarketing spontaneous adverse events in Lilly Clintrace database, Lilly analysis of FDA MedWatch database, literature review and a summary of previously submitted Lilly data. This information was shared with FDA for consideration with their ongoing evaluation of glucose metabolism and the atypical antipsychotics. At this time, no action has been taken by FDA.

Attachment 1
Dear Doctor Letter

Olanzapine Periodic Safety Update
01 April 2002 – 30 September 2002
Eli.Lilly & Co. - Confidential

Page 7

26 September 2002

Addressee's Name
Title
Company Name
Street Address
City State Code
Country

RE: Antipsychotics and diabetes

Dear Doctor:

In recent months, there has been heightened clinical interest in glucose dysregulation (new hyperglycemia and exacerbations of pre-existing diabetes mellitus) and the use of antipsychotic medications. This is associated with the well recognised higher prevalence of diabetes in patients with schizophrenia.^{1,2,3,4} This prevalence could be as much as two to four times greater than the incidence reported in the general population^{5,6,7,8} and occurs in the presence of many confounding variables (including lifestyle, weight, family history etc.).

Eli Lilly and company maintains a comprehensive database of all reported Adverse Events and provides this information to regulatory agencies worldwide in the form of Periodic Safety Update Reports. Additionally, Eli Lilly Australia has pro-actively approached the Australian Therapeutic Goods Administration (TGA) with this information as it pertains to olanzapine (Zyprexa). As a result of our ongoing monitoring activity and Zyprexa Product Information changes in some other countries, Eli Lilly have suggested to the TGA a number of changes to the Zyprexa PI. These changes are outlined below:

The change to the "Precautions" section of the Product Information -

"There is an increased prevalence of diabetes in patients with schizophrenia. As with some other antipsychotics, exacerbation of pre-existing diabetes has been reported very rarely. Hyperglycaemia, diabetic coma and diabetic ketoacidosis have been reported in very rare cases, sometimes in patients with no reported history of hyperglycaemia (see ADVERSE REACTIONS). Appropriate clinical monitoring is advisable in diabetic patients."

Note that "very rare" refers to an incidence <0.01%.

Olanzapine Periodic Safety Update
01 April 2002 – 30 September 2002
Eli.Lilly & Co. - Confidential

Page 8

There is also a change to the “Adverse Events” section of the Product Information -

Adverse Events identified from clinical trials

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;

Adverse Events identified from spontaneous post marketing surveillance

Metabolic - Very rare ($< 0.01\%$): exacerbation of pre-existing diabetes

These changes to the Zyprexa Product Information have been accepted by the TGA.

To place these changes in perspective, we have attached for your information, the relevant sections concerning glucose dysregulation from the Product Information of other atypical and typical antipsychotics.

We would be happy to provide further information on request.

Yours sincerely

Ray Parkin MB BS, FRACP, M.A. (Ethics), M.Med
Medical Director
Eli Lilly Australia Pty Ltd

Attachment: Table 1. Antipsychotics: Current Adverse Events and Precautions sections relating to glucose dysregulation (as shown in Approved Product Information).

For further information on the medications listed below please contact the manufacturing company. This list is not presented as a comparison of risk but simply to highlight the occurrence of glucose dysregulation as a side effect of many antipsychotic medications.

This list is current as at 18 September 2002.

Table 1. Antipsychotics: Current Adverse Events and Precautions sections relating to glucose dysregulation (as shown in Approved Product Information).

Class	Compound	Brand name	Company	Product Information
<i>Atypical</i>	clozapine	Clozaril	Novartis	<u>Adverse Events</u> Endocrine. Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported rarely during Clozaril treatment in patients with no prior history of hyperglycaemia.
	risperidone	Risperdal	Janssen-Cilag	<u>Adverse Events</u> Hyperglycaemia and exacerbations of pre-existing diabetes have been reported in very rare cases during risperidone treatment.
<i>Typical</i>	chlorpromazine hydrochloride	Largactil	Aventis Pharma	<u>Adverse Events</u> Endocrine. Elevated prolactin levels, impaired thermoregulation, hyperglycaemia, other hypothalamic effects.
	droperidol	Droleptan Injection	Pharmalab	<u>Adverse Events</u> Endocrine. Other endocrine adverse effects include impotence, increased libido, hyperglycaemia and hypoglycaemia.
	flupenthixol decanoate	Fluanxol	Lundbeck	<u>Adverse Events</u> Metabolic and endocrine. Related drugs have also been associated with false positive pregnancy tests, peripheral oedema, gynaecomastia, hypoglycaemia, hyperglycaemia and glycosuria.
	fluphenazine	Fluphenazine	David Bull	<u>Adverse Events</u>

	decanoate	decanoate oily injection		Metabolic and endocrine. Alterations may occur in blood glucose levels leading to loss of diabetic control.
Class	Compound	Brand name	Company	Product Information
<i>Typical (cont)</i>	haloperidol	Serenace	Sigma	Adverse Events Endocrine effects. Hyperprolactinaemia, gynaecomastia, menstrual irregularities including oligomenorrhoea or amenorrhoea, mastalgia, breast engorgement, impotence or increased libido, lactation, hyperglycaemia, hypoglycaemia, hyponatraemia, inappropriate antidiuretic hormone secretion (very rare).
	haloperidol decanoate	Haldol decanoate	Janssen-Cilag	Adverse Events Endocrine. Hypoglycaemia, hyperglycaemia or hyponatraemia are rare.
	haloperidol decanoate	Haloperidol decanoate oily injection	Janssen-Cilag	Adverse Events Endocrine. Hypoglycaemia, hyperglycaemia or hyponatraemia are rare.
	pimozide	Orap	Janssen-Cilag	Adverse Events Endocrine. Endocrine effects noted in association with the use of other neuroleptics include false positive pregnancy tests, gynaecomastia, inhibition of ejaculation, mastalgia, breast engorgement, increased libido, hyperglycaemia and hypoglycaemia.
	thiordazine; thioridazine hydrochloride	Melleril	Novartis	Interactions Antidiabetic agents. Phenothiazines affect carbohydrate metabolism and may, therefore, interfere with control of blood sugar in diabetic patients.
	trifluoperazine hydrochloride	Stelazine	Link	Adverse Events Endocrine. Hyperglycaemia, hypoglycaemia, glycosuria, lactation, galactorrhoea, gynaecomastia, elevated prolactin levels, amenorrhoea, false positive pregnancy tests.
	zuclopenthixol	Clopixol	Lundbeck	Adverse Events

	decanoate			Metabolic and endocrine. Related drugs have been associated with breast enlargement, menstrual irregularities, false positive pregnancy tests, peripheral oedema, hypoglycaemia and hyperglycemia and glycosuria.
--	-----------	--	--	---

References:

1. *Cagliero E, Henderson DC, Nathan DM*
Diabetic Ketoacidosis in Patients with Schizophrenia Disorders
APA Annual Meeting, May 2001, New Orleans LA. Institute of Psychiatric Services Meeting, October 2001, Orlando FL.
2. *Newcomer JW, Fucetola R, Haupt DW, Melson AK, Schweiger JA, Cooper BP, Selke G*
Glucose Metabolism During Antipsychotic Treatment in Schizophrenia
International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.
3. *Goldman M, Milner KK, Shriberg RF*
Glucose Metabolism and the Treatment of Schizophrenia: A Complex Relationship
Institute of Psychiatric Services Meeting, October 2001, Orlando FL.
4. *Casey DE, Danielson EM, Fishman NB.*
Prevalence of Diabetes in Schizophrenia Patients Treated with Antipsychotics
APA Annual Meeting, May 2001, New Orleans LA
5. *Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio.*
Diabetes mellitus in schizophrenic patients.
Compr Psychiatry. 1996; 37:68-72.
6. *Keskiner A, Toumi AE, Bousquet T.*
Psychotropic drugs, diabetes, and chronic mental patients.
Psychosomatics. 1973; 16:176-181.
7. *McKee HA, D'Arcy PFD, Wilson PJK.*
Diabetes and schizophrenia: a preliminary study.
J Clin Hosp Pharmacy. 1986; 11:297-299.
8. *Mukherjee S.*
High prevalence of type II diabetes in schizophrenic patients.
Schizoph Res. 1995;15:195 (abstr).

APPENDIX 1

Olanzapine Cumulative Summary of Worldwide Market Authorisation Status

APPENDIX 2

Update on Regulatory or Marketing Authorisation Holders' Actions taken for Safety Reasons.

During the period covered by the report (1 April 2002 to 30 September 2002), the following label changes have been made by type II variation for safety reasons:

- Zyprexa (EMEA/H/C/115/II/32), Olansek (EMEA/H/C/115/II/24), Zyprexa Velotab (EMEA/H/C/115/II/09).

The following safety changes were made to the Zyprexa SmPC (corresponding changes were also made for Olansek and Zyprexa Velotab).

Under **Section 4.4 Special warnings and special precautions for use**, the following text was added.

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly. Gradual dose reductions should be considered when discontinuing olanzapine.

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see also 4.8 Undesirable Effects), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medications (dopamine agonist) and to remain on the same anti-Parkinsonian medications and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Under **Section 4.4 Special warnings and special precautions for use**, the following phrase "in patients receiving medicines known to cause neutropenia" was added to the paragraph below. In addition, the following text was deleted from this paragraph "Thirty-two patients with clozapine related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts."

As with other neuroleptic medicines, caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see Section 4.8).

Under **Section 4.5 Interaction with other medicinal products and other forms of interaction**, "or ketoconazole" was deleted as an example of CYP1A2 inhibitors in the following text.

Inhibition of CYP1A2: Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female nonsmokers and 77 % male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Under **Section 4.6 Pregnancy and lactation**, the following text was added.

Spontaneous reports have been very rarely received on tremor, hypertonia, lethargy and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

Under **Section 4.7 Effects on ability to drive and use machines**, “and dizziness” was added to the following text.

Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

Under **Section 4.8 Undesirable effects**, the following text was added.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson’s disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

Under **Section 4.8 Undesirable effects** in the table of undesirable effects based on post-marketing spontaneous reports, the following text was added.

Blood and lymphatic system disorders: Very rare (<0.01%): Neutropenia

Immune System Disorders: Very rare (<0.01%): Allergic reaction (e.g. anaphylactoid reaction, angioedema, pruritis or urticaria).

Nervous system disorders: Very rare (<0.01%): Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely when olanzapine is stopped abruptly.

Renal and Urinary Disorders: Very rare (<0.01%): Urinary Hesitation



The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

London, 19 September 2002
Doc. Ref.: EMEA/Ho/23341/02

Dr. John Saunders
European Regulatory Affairs
Eli Lilly & Company Limited
Lilly Research Centre
Erl Wood Manor
Sunninghill Road
Windlesham
Surrey, GU20 6PH

Dear Dr. Saunders,

Subject: Outcome of the discussions at the September 2002 CPMP and PhVWP plenary meetings on olanzapine and diabetes

The CPMP and PhVWP have reviewed in their September 2002 meetings the results of a recently published study (Koro *et al.*, BMJ 2002; 325: 243) which suggests that olanzapine treatment is associated with a higher risk of incident diabetes mellitus compared to non-use of neuroleptics and to conventional neuroleptic use. Furthermore, the results suggest that the risk of incident diabetes may be higher in patients who are using olanzapine compared to risperidone. These results are in partial contrast to the results of UK GPRD and US Advance PCS database analyses which were previously presented to the CPMP by the Marketing Authorisation Holder.

The MAH is asked to comment on the results of the Koro *et al.* study and to present an overall analysis of the risk of incident diabetes mellitus during olanzapine treatment compared to other atypical neuroleptics and conventional neuroleptics. This analysis should include the results from other available pharmacoepidemiological studies and take into account the impact of the presence or absence of risk factors for the development of diabetes mellitus.

The MAH should evaluate the impact of the SPC changes introduced as regards the occurrence of diabetes mellitus on reporting of serious outcomes.

The MAH is asked to provide the review within 2 months.

Yours sincerely,

Dr. Panos Tsintis
Head of Sector
Post-authorisation Evaluation of Medicines for Human Use

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int www.emea.eu.int