

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%.

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

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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 decanoate	Fluphenazine decanoate oily injection	David Bull	<u>Adverse Events</u> 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	<u>Adverse Events</u> 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	<u>Adverse Events</u> Endocrine. Hypoglycaemia, hyperglycaemia or hyponatraemia are rare.
	haloperidol decanoate	Haloperidol decanoate oily injection	Janssen-Cilag	<u>Adverse Events</u> Endocrine. Hypoglycaemia, hyperglycaemia or hyponatraemia are rare.
	pimozide	Orap	Janssen-Cilag	<u>Adverse Events</u> 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	<u>Interactions</u> Antidiabetic agents. Phenothiazines affect carbohydrate metabolism and may, therefore, interfere with control of blood sugar in diabetic patients.
	trifluoperazine hydrochloride	Stelazine	Link	<u>Adverse Events</u> Endocrine. Hyperglycaemia, hypoglycaemia, glycosuria, lactation, galactorrhoea, gynaecomastia, elevated prolactin levels, amenorrhoea, false positive pregnancy tests.
	zuclopenthixol	Clopixol	Lundbeck	<u>Adverse Events</u>

	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.
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