

To: CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=Lisa A Vierhile/OU=AM/O=LLY@Lilly;
CN=Charles Zezza/OU=AM/O=LLY@Lilly
CC: CN=Anthony J Bonnici/OU=AP/O=LLY@Lilly; CN=Peter Clark/OU=AP/O=LLY@Lilly; CN=Jo M
Inder/OU=AP/O=LLY@Lilly; CN=Katarina Kelin/OU=AP/O=LLY@Lilly; CN=Paul
Major/OU=AP/O=LLY@Lilly; CN=Kylie J Murray/OU=AP/O=LLY@Lilly; CN=Raymond
Parkin/OU=AP/O=LLY@Lilly; CN=Sue M Rambaud/OU=AP/O=LLY@Lilly
Date: 07/29/2002 03:43:57 AM
From: CN=Julie A Rikard-Bell/OU=AP/O=LLY
Subject: Zyprexa PI - Diabetes Statement - TGA Response

Patrizia, Lisa and Charlie,

We have received a fax from the TGA today responding to our suggested wording re diabetes in the Zyprexa PI.

The wording we submitted was:-

Precautions

There is an increased prevalence of diabetes in patients with schizophrenia. Exacerbation of pre-existing diabetes has been reported very rarely. Appropriate clinical monitoring is advisable in diabetic patients.

Adverse Reactions

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 11mmol/L (suggestive of potential diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels 8.9mmol/L but <11mmol/L (suggestive of potential hyperglycaemia) was 2.0%, compared to 1.6% with placebo; random triglyceride levels 2 times the upper limit of fasting normal have been seen occasionally (1.9% incidence) in clinical trials (N=107) with no observed cases > 3 times the upper limit of fasting normal in these trials.

The TGA is requesting that we change the wording to:-

Precautions

There is an increased prevalence of diabetes in patients with schizophrenia. 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.

For Adverse Reactions, they have asked that we remove the word potential and include exacerbation of pre-existing diabetes in the post marketing ADRs..

Adverse Reactions

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 ~~potential~~ 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 ~~potential~~ hyperglycaemia) was 2.0%, compared to 1.6% with placebo; random triglyceride levels ≥ 2 times the upper limit of fasting normal have been seen occasionally (1.9% incidence) in clinical trials (N=107) with no observed cases > 3 times the upper limit of fasting normal in these trials.

Adverse events identified from spontaneous post marketing surveillance

Metabolic - Very rare ($< 0.01\%$): hyperglycaemia; diabetic coma; diabetic ketoacidosis; hypertriglyceridemia, exacerbation of pre-existing diabetes.

We have been asked to submit a revised PI with the requested changes within 2 weeks.

Charlie, I will forward the TGA fax on to you.

Best regards,
Julie

Julie Rikard-Bell
Regulatory Affairs Manager
Eli Lilly Australia Pty Limited

E-mail: rikard-bell_julie_a@lilly.com
Phone: 61 2 9325 4459
Fax: 61 2 9325 4688

To: CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly
Date: 08/12/2002 03:59:35 PM
From: CN=James A Edwards/OU=AM/O=LLY
Subject: oral hypoglycemic agents & antipsychotic therapy
Attachments: hyp_aa memo request.doc

Patrizia,

See attached. This was something that Mark asked me to provide to you, prior to getting side-tracked with the South Africa business.

Please comment/edit.

Thanks,

Jamie



hyp_aa memo request.doc

James A. Edwards, Pharm.D., Ph.D.
Critical Issues - Customer Response Team
Zyprexa Product Team
317.651.1721