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The Managing Director
Eli Lilly Australia Pty Ltd
112 Wharf Road
WEST RYDE NSW 2114

Attn: Ms Kylie Murray
Senior Regulatory Affairs Associate

Dear Sir/Madam,

ZYPREXA (Olanzapine)- Japanese Label Changes

I refer to your reply dated 26 April 2002 to our letter dated 18 April 2002 regarding the Japanese label changes for Zyprexa relating to hyperglycaemia and diabetes mellitus.

The data provided with your response has been reviewed and the following comments have been noted:

- The European Union SmPC contains an expanded discussion on this issue in their precautions and undesirable effects sections, however the Australia PI document contains no precaution on this issue.

- The Japanese Ministry of Health, Labor and Welfare has significantly updated their Zyprexa label regarding hyperglycaemia and diabetes and mandated a Dear doctor Letter be sent to physicians.

- The FDA are reviewing the issue and the EMEA have requested a discussion of the issue in the next periodic safety update report due May 2002.

- The Olanzapine Clinical Trial Database observed mean glucose increases of 0.8mg/dL at 18 weeks and 4.6mg/dL at 52 weeks, which was significantly greater than that observed with haloperidol or placebo.

- The Advance PCS prescription database showed the incidence of diabetes mellitus was significantly increased in the olanzapine group compared to the general PCS population (HR 3.0 [2.6-3.5], $p \leq 0.0001$), with similar increases seen for other antipsychotics. However the UK-GPRD showed no significant difference from the general GPRD population but this was limited by cohort sample size (HR 2.0 [0.3-14.5], $p=0.48$).

- As of 30 Sep 2001, there were 743 adverse events reported involving glucose dysregulation, including 36 deaths. Of the 9 Japanese cases there were 2 deaths, although there were confounding factors.

- Of the 768 adverse events reported on the ADRAC database, there were 8 diabetes mellitus, 1 diabetes mellitus aggravated, 5 hyperglycaemia and 2 glucose tolerance abnormal.

Based on these findings from the data submitted, it is recommended that the Australian PI document for Zyprexa be updated to include similar information as that presented in the European Union SmPC. Specifically, the underlined information presented in Section 4.4 "Special Warnings and special precautions

for use" and Section 4.8 "Undesirable effects" of the EU SmPC provided in your response should be included in the Australian PI document. Please submit a safety related notification, pursuant to Section 32(4) of the *Therapeutic Goods Act 1989*, to include the requested information. Such a notification should be submitted by 14 June 2002.

If you wish to discuss this issue, please do not hesitate to contact either myself on (02) 6232 8356 or the Head of Clinical Evaluation Unit 1, Dr Phillip Chipman on (02) 6232 8113.

Yours Sincerely

Jason Ferla

Dr Jason Ferla
Clinical Evaluation Unit 1
Drug Safety & Evaluation Branch

10 May 2002