

8<sup>th</sup> March, 2004

Dear Doctor,

**Re: Important Safety Information on Olanzapine and Risk of Mortality and Stroke in Elderly Patients with Dementia-Related Psychosis and/or Behavioural Disturbances**

In agreement with the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMA) and the Irish Medicines Board, Eli Lilly and Co (Ireland) Ltd. is writing to inform you of important new safety information regarding olanzapine and its use in *elderly patients with dementia*. **Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients.**

**Elderly patients being treated with olanzapine for dementia-related psychosis and/or behavioural disturbances should have their treatment reviewed and discussed with them and/or their carers.**

**This safety information is derived from clinical trials and is relevant to elderly patients with dementia being treated with olanzapine. There are two components of the safety information:**

- 1) A two-fold increase in mortality compared with placebo**
- 2) A three-fold increase in cerebrovascular adverse events compared with placebo**

This information is based upon an integrated review and analysis of 5 placebo-controlled studies (N=1662; olanzapine n=1184, placebo n=478) conducted by Eli Lilly with olanzapine in elderly patients with dementia (Alzheimer's, vascular, and mixed). The efficacy of olanzapine in the treatment of psychosis and/or behavioural symptoms was not established in these studies.

The new safety data have been submitted to the CPMP (the European scientific committee for products authorised throughout Europe, such as Zyprexa) and the following recommendations have been made to update the wording in the Summary of Product Characteristics (SPC) and the Package Leaflet (PL) for all formulations and presentations of Zyprexa and Zyprexa Velotab.

The following changes have been introduced in the SPC:

#### 4.4 Special warnings and special precautions for use

*Olanzapine is not approved for the treatment of dementia related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age >65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.*

*In the same clinical trials, cerebrovascular adverse events (CVAE, e.g., stroke, transient ischaemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced CVAE had pre-existing risk factors. Age >75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.*

#### 4.8 Undesirable effects

*In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse events compared to placebo (see also 4.4). Very common (>10%) undesirable effects associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia and urinary incontinence were observed commonly (1-10%).*

The following changes have been introduced in the PL:

#### 2. Take special care with Zyprexa:

- *The use of Zyprexa in elderly patients with dementia is not recommended as it may have serious side effects*

*If you suffer from any of the following illnesses tell your doctor as soon as possible:*

- *Stroke or 'mini' stroke*

*If you suffer from dementia, you or your carer/relative should tell your doctor if you have ever had a stroke or 'mini' stroke.*

#### 4. Possible side effects

*While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls and have trouble walking. Some fatal cases have been reported in this particular group of patients.*

You can assist the monitoring of the safety of Zyprexa/ Zyprexa Velotab by reporting adverse reactions, which should be sent to Eli Lilly & Co (Ireland) Ltd., Hyde House, 65 Adelaide Rd., Dublin 2, or by phone to 0044 1256 315999 or to the Irish Medicines Board.

The EMEA have provided a statement relating to this safety information and this will be available on their website (<http://www.emea.eu.int/hums/human/drugalert/drugalert.htm>) at 13:00 GMT on the 9<sup>th</sup> March. This provides further information on the findings of the EMEA and its scientific committee, the CPMP, on this issue.

Should you have any questions or concerns regarding this important safety information, please contact the Eli Lilly medical information department at Tel: 0044 1256 775000.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Anne Tobin', is written over a horizontal line.

Dr. Anne Tobin  
Medical Director  
Eli Lilly & Co (Ireland) Ltd.