The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

EMBARGO DATE AND TIME: 9 March 2004, 13:00 (UK Time)

London, 9 March 2004

Doc. Ref: EMEA/CPMP/856/04/Final

EMEA PUBLIC STATEMENT ON THE SAFETY OF OLANZAPINE (Zyprexa, Zyprexa Velotab)[1]

Cerebrovascular adverse events and increased mortality in elderly patients with dementia

The EMEA and its scientific committee, the CPMP, have been made aware of important new safety information relating to the use of olanzapine[2] in dementia. These data from clinical trials show an increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia receiving olanzapine. Healthcare professionals should be made aware that **olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and that it is not recommended for use in this particular group of patients.**

A series of clinical trials in elderly patients (aged over 65 years) with dementia has shown an approximately two-fold increase in mortality and a three-fold increase in cerebrovascular adverse events for olanzapine compared to placebo. The higher mortality was not associated with olanzapine dose or duration of treatment, but predisposing risk factors such as age (over 65 years), sedation, dysphagia, malnutrition and dehydration, baseline pulmonary conditions (pneumonia with or without aspiration), or concomitant use of benzodiazepines were found to be associated with the higher risk of death. The data also showed that underlying vascular dementia was significantly associated with a greater likelihood of cerebrovascular adverse events. The efficacy of olanzapine was not established in these trials.

The CPMP reviewed these data in the wider context of atypical antipsychotic usage in patients with dementia.

Based on the clinical trial findings for olanzapine, the CPMP has decided to introduce relevant warnings to prescribers and patients in the product information for olanzapine.

In view of the seriousness of these reactions, the EMEA wishes to draw attention to the following important safety information to physicians:

- Olanzapine is not indicated for the treatment of patients with dementia-related psychosis and/or disturbed behaviour.
- Because of the identified risks, patients currently receiving olanzapine for dementia-related psychosis and/or disturbed behaviour should have their treatment reviewed by their physician.
- Neuroleptics are known to be used in patients with dementia who experience psychotic symptoms and disturbed behaviour. There are insufficient data to confirm any difference in the risk of mortality or cerebrovascular accidents among atypical neuroleptics, including olanzapine, or between atypical and conventional neuroleptics. Physicians should be aware that the risks identified for olanzapine cannot be excluded for other atypical or conventional neuroleptics.

---

[1] There are two medicinal products containing olanzapine authorised in the EU, Zyprexa and Zyprexa Velotab, authorised on 27 September 1996 and 3 February 2000, respectively. The Marketing Authorisation Holder for both products is Eli Lilly. Olanzapine is currently marketed in all EU Member States, as well as in Norway and Iceland.

[2] Olanzapine tablets are indicated for the treatment of schizophrenia and for the treatment of moderate to severe manic episode, and for the prevention of recurrence of bipolar disorder. Olanzapine powder for solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate.
Olanzapine is not indicated for the treatment of patients with dementia-related psychosis and/or disturbed behaviour.

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 http://www.emea.eu.int

Information for elderly patients with dementia taking olanzapine, their relatives and carers

- Olanzapine is not approved for use by patients with dementia. Clinical trials in elderly patients with dementia have shown serious side effects such as stroke.
- Patients already receiving olanzapine for treatment of some symptoms related to dementia should consult their physician in order to have their treatment reviewed.

As an urgent measure, the prescribing and patient information of olanzapine have been modified through a rapid procedure at the request of the Marketing Authorisation Holder. Relevant changes to the product information are indicated in Annex 1. For the scientific evaluation of Zyprexa and Zyprexa Velotab and the complete revised product information, please consult the European Public Assessment Report also available on the EMEA Website.

For further information contact:

Mr Noël Wathion

Head of Unit

Post-Authorisation Evaluation of Medicines for Human Use (Tel: +44 20 7418 8592, Fax: + 44 20 7418 8668)

ANNEX I

PROVISONAL CHANGES INTRODUCED

TO INFORMATION FOR PRESCRIBERS AND PATIENTS

Zyprexa 2.5 mg tablet as relevant example

INFORMATION TO PRESCRIBERS (SUMMARY OF PRODUCT CHARACTERISTICS)

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%).

INFORMATION TO PATIENTS (PACKAGE LEAFLET)

2. Before you take Zyprexa

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.