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IMPORTANT DRUG SAFETY INFORMATION

March 10, 2004

**SUBJECT: ZYPREXA* (olanzapine) and Cerebrovascular
Adverse Events in Placebo-Controlled Elderly Dementia Trials**

Dear Healthcare Professional:

Eli Lilly Canada Inc., following discussions with Health Canada, would like to inform you of important new safety information pertaining to cerebrovascular adverse events that have occurred in elderly patients with dementia-related psychosis treated with ZYPREXA (olanzapine) in clinical trials. ZYPREXA is not approved for use in elderly patients with dementia-related psychosis.

CEREBROVASCULAR ADVERSE EVENTS

Summarized clinical trial data are provided in the "Background Information" section of this letter.

Recent analysis of some clinical trials in elderly patients with dementia suggests that the use of ZYPREXA in these patients may be associated with an increased incidence of reports of cerebrovascular adverse events (CVAEs) such as stroke and transient ischemic attacks (TIAs), including few fatalities.

While elderly patients are at an increased risk of CVAEs, the above clinical trial data reflect an increased incidence of such adverse events in patients taking ZYPREXA compared with placebo-treated dementia patients after adjusting for age, gender, and type of dementia.

Physicians are advised to assess the risks and benefits of the use of ZYPREXA in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient.

Physicians should counsel their patients/caregivers to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems, so that diagnosis can be made and treatment options considered, including discontinuation, without delay.

There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with ZYPREXA or all antipsychotic agents. Clinical trial data appear to suggest that patients with a dementia diagnosis of vascular or mixed type had a higher likelihood of experiencing CVAEs than other types of dementia.

BACKGROUND INFORMATION

Clinical Trial Data Available to Date:

This data is based upon an integrated analysis of 5 placebo-controlled studies investigating the incidence of CVAE in elderly patients with dementia-related psychosis (Alzheimer's, vascular, and mixed) (olanzapine n=1178; placebo n=478) conducted by Lilly with ZYPREXA (Table 1). The efficacy of ZYPREXA in elderly patients who have dementia-related psychosis has not been established in clinical trials.

Table 1. Incidence of reported CVAEs in placebo-controlled, dementia trials in elderly patients taking ZYPREXA.

Study No.	ZYPREXA	PLACEBO
	Patients with CVAEs	Patients with CVA Es
HGAO	0% (0/118)	0.8% (1/118)
HGEU	0.6% (1/159)	0% (0/47)
HGGU	2.5% (5/204)	0% (0/94)
HGIC	2.8% (5/177)	1.1% (1/90)
HGIV	0.8% (4/520)	0% (0/129)
Total	1.3% (15/1178)	0.4% (2/478)

Four patients died in the ZYPREXA group versus 1 patient in the placebo group. In open-label safety trials in dementia patients (N=231), studied for up to 59 weeks, 7 cases of CVAEs, including 2 fatalities, were reported.

In double-blind, placebo-controlled trials, patients with a dementia diagnosis of vascular or mixed type had approximately a 5-fold higher likelihood of experiencing CVAEs than did patients with a diagnosis of Alzheimer's.

Spontaneous Post-marketing Reports:

ZYPREXA is approved for the treatment of schizophrenia and related psychotic disorders and acute bipolar mania. However, it is not approved for use in elderly patients with dementia-related psychosis.

Physicians are reminded to assess and counsel patients/caregivers of risk factors associated with an increased risk for a CVAE (e.g. history of previous CVAE or transient ischemic attack, hypertension, cigarette smoking) and concurrent medical conditions and/or concomitant medications that have a temporal association with CVAE.

This safety information reconfirms the need for careful patient assessment and consideration of risk factors in the treatment of elderly patients with dementia-related psychosis.

Eli Lilly routinely assesses safety information as it becomes available and updates Product Monographs accordingly. Eli Lilly Canada Inc. is committed to providing you with the most current and complete product information available for the management of patients receiving ZYPREXA.

Eli Lilly Canada Inc. is working with Health Canada to update the Canadian Prescribing Information. In the interim, Eli Lilly Canada Inc. would like to remind you of the current wording in the "Precautions"

section of the Canadian ZYPREXA (olanzapine) Prescribing Information which refers to cerebrovascular disease:

“ZYPREXA should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).”

A copy of the revised Prescribing Information will be provided to you at your request as soon as it becomes available. Please call Eli Lilly Canada Inc at 1-888-545-5972.

The identification, characterization and management of drug-related adverse events are dependent on the active participation of Healthcare Professionals in adverse event reporting programs. Any occurrences of CVAEs or other serious and/or unexpected adverse events in patients receiving ZYPREXA should be reported to Eli Lilly Canada Inc. at the following address, or to the Bureau of Licensed Product Assessment, at the address at the end of the letter:

Customer Response Centre
Eli Lilly Canada Inc.
3650 Danforth Avenue
Toronto, Ontario
M1N 2E8
Toll Free Number: 1-888-545-5972
Fax: 1-888-898-2961

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Sincerely,



Loren D. Grossman, MD, FRCPC, FACP
Vice President, Research and Development
Eli Lilly Canada Inc.

Any suspected adverse reactions in patients receiving ZYPREXA* (olanzapine) can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the TPD website or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

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