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IMPORTANT DRUG SAFETY INFORMATION FOR PROZAC:
Stronger WARNING for SSRIs and other newer anti-depressants regarding the potential for behavioural and emotional changes, including risk of self-harm

May 18, 2004

Dear Healthcare Professional:

Eli Lilly Canada Inc., following discussions with Health Canada, would like to inform you of important safety information regarding the possibility that SSRIs (selective serotonin reuptake inhibitors) and other newer anti-depressants may be associated with behavioural and emotional changes, including risk of self-harm.

The new Class warning incorporated in the product monograph of PROZAC (fluoxetine hydrochloride) is provided below.

POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adult and Pediatrics: Additional data

- **There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms

Patients currently taking SSRIs or other newer anti-depressants should NOT be discontinued abruptly, due to risk of discontinuation symptoms. PROZAC has only rarely been associated with such symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation, except for fluoxetine, is recommended. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy which makes dose tapering unnecessary in most patients taking this drug (see Product Monograph sections PRECAUTIONS: DISCONTINUATION OF TREATMENT WITH PROZAC (POST-MARKETING AND CLINICAL TRIALS); ADVERSE REACTIONS: Discontinuation of Treatment with Prozac (Post-Marketing and Clinical Trials); DOSAGE AND ADMINISTRATION: DISCONTINUATION OF TREATMENT WITH PROZAC).

It should be noted that a causal role for SSRIs and other newer anti-depressants in inducing self-harm or harm to others has not been established. The possibility of a suicide attempt is inherent in depression and other psychiatric disorders, and may persist until remission occurs. Therefore, high-risk patients should be closely supervised throughout therapy with appropriate consideration to the possible need for hospitalization. The updated warning informs practitioners that all patients being treated with SSRIs and other newer anti-depressants should be rigorously monitored for clinical worsening, or onset/worsening of agitation-type adverse events, or other indicators of potential for suicidal behaviour.

Fluoxetine is not indicated for use in the pediatric population.

New Information Added to the Consumer Information Section

The Consumer Information Section of the product monograph has been updated to reflect this new Class warning, and to advise patients that treatment with SSRIs and other newer anti-depressants is most safe and effective when there is good communication with the treating physician about how the patient is feeling.

Background

In February 2004, a scientific advisory panel set up by Health Canada was asked to provide the clinical practice perspective on the pediatric clinical trial safety data, and the spontaneous post-marketing reports for SSRIs and other newer antidepressants. The panel agreed that a contraindication was not warranted for these medications, and supported Health Canada's recommendation for stronger warnings, while providing suggestions and comments. The record of proceedings, and other information about the panel, can be found on Health Canada's website at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sap_ssri_2004-02-20_rop_e.html.

Eli Lilly Canada Inc. continues to work closely with Health Canada to monitor adverse event reporting and to ensure that up-to-date information regarding the use of PROZAC (fluoxetine hydrochloride) is available.

The identification, characterization and management of drug-related adverse events are dependent on the active participation of healthcare professionals in adverse drug reaction reporting programs. Health care professionals are asked to report any suspected adverse reactions in patients receiving PROZAC (fluoxetine hydrochloride) directly to Eli Lilly Canada Inc. or Health Canada at the following addresses:

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

Any suspected adverse reaction 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
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

For other inquiries: please refer to contact information

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

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.

Inquiries from healthcare professionals should be directed to Eli Lilly Canada Customer Response Centre at 1-888-545-5972 between 8 a.m. and 6 p.m. EST.

Sincerely,

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