Health Canada Endorsed Important Safety Information on CELEXA® (citalopram hydrobromide)

January 25, 2012

Dear Healthcare Professional,

Subject: Association of CELEXA® (citalopram hydrobromide) with Dose - Dependent QT Prolongation

Lundbeck Canada, in collaboration with Health Canada, would like to inform you that the antidepressant Celexa® (citalopram hydrobromide; also marketed as generics), should no longer be used at doses greater than 40 mg per day due to study results indicating a dose-dependent potential for QT prolongation. Previously, the Celexa® (citalopram hydrobromide) Canadian Product Monograph stated that certain patients may require 60 mg per day.

Celexa® (citalopram hydrobromide) is a selective serotonin reuptake inhibitor (SSRI) indicated for the symptomatic relief of depressive illness. It is available as 20 mg and 40 mg tablets.

- A thorough QT study, conducted according to international standards, assessing the effects of citalopram 20 mg per day and 60 mg per day on the QT interval has shown that citalopram causes dose-dependent QT prolongation.
- Celexa® (citalopram hydrobromide) should no longer be prescribed at doses greater than 40 mg per day.
- 20 mg per day is the maximum recommended dose for patients with hepatic impairment, patients who are 65 years of age or older, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor.
- Celexa® (citalopram hydrobromide) is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation.

A randomized, double-blind, placebo- and positive-controlled, crossover study was performed in healthy subjects (N=119) to examine the effects of citalopram 20

mg/day and 60 mg/day on electrocardiogram (ECG) intervals (individually corrected QTcNi interval) when administered according to an escalating multiple dose regimen (9 days at 20 mg/day, 4 days at 40 mg/day, 9 days at 60 mg/day). The maximum mean (upper bound of the 95% one-sided confidence interval) differences from placebo were 8.5 (10.8) and 18.5 (21.0) msec for 20 mg and 60 mg citalopram, respectively. The effects of the 40 mg/day dose were not studied, but are predicted to be approximately 13 msec (estimate value on QTcNi).

Changes in the electrical conductivity of the heart (prolongation of the QT interval on the ECG) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal.

ECG monitoring is recommended in patients with risk factors for Torsade de Pointes such as congestive heart failure, recent myocardial infarction, bradyarrhythmias or in patients taking concomitant medications that prolong the QT interval as well as in patients with altered citalopram metabolism (e.g. liver impairment).

Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low blood levels of potassium and magnesium.

Hypokalemia and hypomagnesemia should be corrected before administering Celexa®(citalopram hydrobromide).

Patients should be advised to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking Celexa®(citalopram hydrobromide). These include dizziness, palpitations, syncope or seizures.

Patients should be cautioned not to stop taking Celexa® (citalopram hydrobromide) or to change the dose without first consulting their healthcare professional. Withdrawal symptoms such as dizziness, feelings of agitation or anxiety, difficulty concentrating, abnormal dreams, nausea or vomiting may occur when SSRI treatment is discontinued, particularly if this is abrupt.

In the event that Celexa® (citalopram hydrobromide) is discontinued or the dose is reduced, healthcare professionals should monitor patients closely for the re-emergence or worsening of any symptoms of depression.

The Canadian Product Monograph for Celexa® (citalopram hydrobromide) has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation.

Lundbeck is working closely with Health Canada to determine if there is a need to include further information regarding QT prolongation in addition to that already present in the labelling for Cipralex® (escitalopram oxalate), a drug related to Celexa® (citalopram hydrobromide).

Managing marketed health product-related adverse reactions depends on health

care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of QT interval prolongation and Torsade de Pointes or other serious or unexpected adverse reactions in patients receiving Celexa® (citalopram hydrobromide) should be reported to Lundbeck Canada or Health Canada at the following addresses:

Lundbeck Canada Inc.
1000 de la Gauchetière St. W., Suite 500
Montreal, Quebec
Canada H3B 4W5
Toll-free : 1 866-880-4636

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Product Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: (613) 954-6522
Fax: (613) 952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

Sincerely,

original signed by

Marie Gagné
Vice-President, Scientific Affairs