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26 October 2011

Dear Healthcare Professional,

Association of CIPRAMIL® (citalopram) with dose-dependent QT interval prolongation

Lundbeck Ireland, in collaboration with the Irish Medicines Board, would like to inform you of important new recommendations for the use of the antidepressant CIPRAMIL® (citalopram, also marketed as generics).

Summary:

- **Citalopram is associated with dose-dependent QT interval prolongation**
- **The maximum dose of citalopram is now 40 mg daily**
- **In the elderly and in patients with reduced hepatic function the maximum dose is lowered to 20 mg daily**
- **Citalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome**
- **Use of citalopram with other medicinal products known to prolong the QT interval is contraindicated**
- **Caution is advised in patients at higher risk of developing Torsade de Pointes, for example those with congestive heart failure, recent myocardial infarction, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines**

Further information of the safety concern

Citalopram is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence. It is also indicated in the treatment of panic disorder and is available as 10 and 20 mg tablets and 40 mg/ml oral drops, solution.

The new recommendations for citalopram-containing products are a result of an assessment of a QT study that has revealed a dose-dependent increase of the QT

interval observed with ECG. In addition, review of data from spontaneous reporting has identified cases of QT prolongation and ventricular arrhythmia including Torsade de Pointes. Further, studies have not shown an added benefit in the treatment of depression at doses higher than 40 mg daily.

The product information of Cipramil as well as the product information of its generics will be revised to include information about the risk for QT interval prolongation and the following new dosage and usage recommendations:

- A study was conducted assessing the effects of 20 mg and 60 mg citalopram on the QT interval in healthy adults. Compared to placebo, the mean change from baseline in QTcF (Fridericia correction) was 7.5 msec at the 20 mg daily dose and 16.7 msec at the 60 mg daily dose
- The study results indicate that citalopram causes dose-dependent QT interval prolongation
- The recommended maximum dose in adults has been lowered from 60 mg to 40 mg daily due to risk of QT interval prolongation with higher doses
- The recommended maximum dose in the elderly is accordingly lowered from 40 mg to 20 mg daily
- The recommended maximum dose is lowered from 30 mg to 20 mg daily in patients with reduced hepatic function
- The product information has also been updated with contraindications, warnings and interactions including:
 - Citalopram has been found to cause a dose-dependent prolongation of the QT interval
 - Cases of ventricular arrhythmia including Torsade de Pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia and with pre-existing QT interval prolongation or other cardiac diseases
 - Citalopram is now contraindicated in patients with known QT interval prolongation and congenital long QT syndrome. Co-administration with another medicinal product that can prolong the QT interval is also contraindicated.
 - Caution is advised in patients at higher risk of developing Torsade de Pointes, for example those with congestive heart failure, myocardial infarction, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines

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 citalopram.

Patients should not stop taking citalopram or change or reduce the dose without first

consulting their Healthcare Professional, as withdrawal symptoms may occur when citalopram treatment is discontinued, particularly if this is abrupt (Refer to the product information for more information regarding withdrawal symptoms).

Healthcare professionals are advised to review patients with doses that are above the now recommended maximum dose and gradually reduce the dose accordingly.

Cases of QT interval prolongation have been reported also in association with some other SSRIs including the S-enantiomer of citalopram (escitalopram). For further information, please refer to the respective product information.

Healthcare Professionals and patients are encouraged to report any product-related adverse reactions to the marketing authorisation holder (see contact details below) or to the IMB using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie.

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Yours faithfully,



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