Annex 2

Summary Assessment Report of the PhVWP October 2011

Citalopram – Risk of QT interval prolongation

Key message

Citalopram may cause QT prolongation and the product information will be updated, in particular to reduce the maximum daily dose to 40mg/day in adults and 20 mg/day in the elderly and patients with impaired liver function.

Safety concern and reason for current safety review

The PhVWP assessed new data from a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 20 and 60 mg citalopram.

The FDA issued an announcement on 24 August 2011, notifying healthcare professionals in the US that citalopram should no longer be used at doses higher than 40 mg/day. The reason was identification of an increased risk for QT interval prolongation. As part of its review, the PhVWP assessed the data which formed the basis for this actionwhich included the results of the above mentioned study.

Clinical setting

Citalopram is indicated for the treatment for depression, panic disorder and obsessive-compulsive disorder (OCD).

QT interval prolongation is an indication of abnormal heart rhythm, which can lead to ventricular arrhythmia, including *torsade de pointes*, and sudden cardiac death.

Information on the data assessed

The PhVWP assessed the results of a randomised, multi-centre, double-blind, placebo-controlled, crossover pharmacokinetic and thorough QT-study undertaken in healthy volunteers given daily doses of 20 and 60 mg citalopram. The PhVWP additionally evaluated data from the marketing authorisation holder of the originator citalopram-containing product in the EU provided in response to a list of question from the PhVWP. Finally, spontaneously reported cases of suspected reactions which could be related to QT interval prolongation were reviewed.

Outcome of the assessment

Following review of the thorough QT-study, the following can be concluded: A dose-dependent increase in QT interval was shown in this thorough QT study, particularly with 60 mg/day.The change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec with 20 mg/day and 16.7 (90%CI 15.0-18.4) msec with 60 mg day. The study was considered of good quality, although testing of a higher dose would have been desirable (in accordance with the ICH E14 guideline). A positive control was included, i.e. moxifloxacin 400 mg/day, which showed expected results, thus confirming assay sensitivity.

Further, the PhVWP considered that cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes were spontaneously reported, predominantly in female patients, with hypokalemia, pre-existing QT interval prolongation or other cardiac diseases. Most of the reported cases of torsade de pointes had a positive dechallenge. Positive rechallenge was also reported. In addition, a number of cases of ventricular arrhythmia, sudden death, loss of consciousness and syncope might also be associated with torsade de pointes. The data from spontaneous reporting also had limitations, for instance underreporting was considered as potentially large for events such as torsades de pointes, cardiac arrhythmia or sudden cardiac death. Thus, those data could not be used to exclude the existence of a risk.

Overall, the PhVWP considered that the results from the study indicated that citalopram causes dose-dependent QT interval prolongation. In considering the appropriate risk minimisation strategy, the PhVWP also noted that elderly patients and patients with reduced liver function achieve higher systemic exposure than younger patients with normal hepatic function. Furthermore, it was also noted that cases of QT-interval prolongation have been reported also in association with some other selective serotonin re-uptake inhibitors (SSRIs) including escitalopram, the S-enantiomer of citalopram.

Based on a review of the available data, the PhVWP concluded that the summary of product information for citalopram-containing medicinal products in the EU should be updated to

- remove the dose recommendation of 60 mg/day;
- limit the maximum daily dose for adults to 40 mg/day;
- limit the daily dose in the elderly and in patients with hepatic impairment to 20 mg/day;
- contraindicate use of citalopram with other medicinal products known to prolong the QT interval;
- include relevant contraindications and warnings; and
- include ventricular arrhythmia including torsade de pointes as adverse reactions.

The package leaflet should be updated accordingly and include advice to patients to

- contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram;
- not to 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;

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