IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

45TH EDITION

Domperidone – Risk of cardiac disorders

(Products include Domerid/Motilium)

Domperidone is a propulsive agent and a dopamine antagonist with antiemetic properties. It is authorised for use in adults for the relief of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents, and in children for the relief of nausea and vomiting.

The risk of QTc prolongation and cardiac risk with domperidone was previously reviewed at EU level by the Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency, with the product information updated to reflect the available data at that time (2008).

In 2010, two new epidemiological studies[1, 2] were published concerning the risk of ventricular arrhythmia or sudden cardiac death (SCD) and a possible association with domperidone. A weak association with SCD was found. It was concluded that there is some evidence to support that, particularly at higher doses (>30mg/day), or in patients >60 years, domperidone may be associated with an increased risk of serious ventricular arrhythmias or SCD.

Spontaneous reports of suspected adverse reactions also suggest a potential association between domperidone and QT prolongation for non-parenteral routes of administration and an association with torsades de pointes (TdP), independently of the route of administration.

Based on the assessment of the available data, the PhVWP recommended further updates to the product information for domperidone-containing products to reflect the current information on the risk of SCD, particularly in patients >60 years and in patients taking daily doses of >30 mg/day and emphasised that domperidone should be used at the lowest effective dose in adults and children.

The PhVWP also recommended that the originator marketing authorisation holder should conduct an additional well-designed, high-powered epidemiological study on the association between domperidone and cardiac disorders, with particular emphasis on dose to further clarify this risk.

Healthcare professionals should be aware of these risks, closely adhere to the recommendations for use and be particularly cautious when advising or treating patients who have existing prolongation of cardiac conduction intervals particularly QTc and those with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

Healthcare professionals are reminded that co-administration with oral ketoconazole, erythromycin or other potent CYP 3A4 inhibitors that prolong the QTc interval should be avoided, for further details see the Summary of Product Characteristics (SPC) on **www.imb.ie**.

This information was also recently communicated in a Direct Healthcare Professional Communication (DHPC) which is available on **www.imb.ie**.

Suspected adverse reactions associated with the use of domperidone including cases of cardiac disorders should be reported to the IMB via the usual routes.

Key Message:
Some epidemiological studies have shown that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. The risk of serious ventricular arrhythmias or sudden cardiac death may be higher in patients >60 years or at daily oral doses >30 mg. Domperidone should be used at the lowest effective dose in adults and children.

References

1. Van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf. 2010; 33: 1003-1014.
2. Johannes C. et al. Pharmacoepidemiology and Drug Safety 2010; 19:881-888.

In this edition

Citalopram and Escitalopram – Risk of QT interval prolongation

(Products include
Cipramil/Ciprager/Ciprotan/ Ciprapine/Citrol
Lexapro/Escipriex/Escitalpro/Escitomar)

Citalopram and escitalopram are selective serotonin reuptake inhibitors (SSRIs) whose indications include treatment of depressive illness and panic disorder (see the individual Summaries of Product Characteristics (SPCs) on www.imb.ie for full details of licensed indications).

Following a review of the available information on the risk of QT prolongation with these medicines, the PhVWP has recommended that the product information for both citalopram and escitalopram be updated with new contraindications and warnings and a reduction in the maximum dose for use in the elderly for both active substances.

For citalopram, there has additionally been a general reduction in the maximum dose and in the maximum dose for patients with impaired liver function.

Advice to Healthcare Professionals:

- Citalopram and escitalopram have been found to cause a dose-dependent prolongation of the QT interval.
- Cases of ventricular arrhythmia including Torsade de Pointes (TdP) have been reported, predominantly in females, with hypokalemia and with pre-existing QT interval prolongation or other cardiac diseases.
- Citalopram and escitalopram are now contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Co-administration with another medicinal product that is known to prolong the QT-interval is also contraindicated. These include Class IA and III antiarrythmics, antipsychotics, tricyclic antidepressants and some antimicrobial agents (eg moxifloxacin, erythromycin IV).
- Caution is advised in patients at higher risk of developing TdP, for example those with congestive heart failure, myocardial infarction, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines.
- Healthcare professionals are advised to review elderly patients treated with citalopram or escitalopram at doses above the new recommended maximum dose, and gradually reduce the dose accordingly (as outlined in the product information to minimise the risk of withdrawal symptoms).

Information on the data assessed

The new recommendations for citalopram-containing products follow an assessment of a QT-study that has revealed a dose dependant 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 TdP. Further, studies have not shown an added benefit in the treatment of depression at doses higher than 40 mg daily. The product information for all citalopram containing products will be revised to reflect the new information regarding the study findings and the following new dosage and usage recommendations:

- The recommended maximumdose of **citalopram** 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 of **citalopram** 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 **citalopram** daily in patients with reduced hepatic function.

In addition to the data evaluated for citalopram, the PhVWP assessed the results of a QT-study undertaken in healthy volunteers given daily doses of 10 and 30 mg escitalopram. The PhVWP concluded that a dose-dependent increase in QT interval was shown in this study, particularly with 30 mg/day. Furthermore, the PhVWP noted that cases of QT interval prolongation and ventricular arrhythmia including TdP were spontaneously reported, predominantly in female patients, with hypokalemia, pre-existing QT interval prolongation or other cardiac diseases. Most of the reported cases of TdP had a temporal relationship with starting treatment with escitalopram, or with the increase in dosing, and/or at the time of other risk situations, e.g. with hypokalaemia. Recovery from the event was reported when escitalopram was discontinued in most of the reported cases. The data from spontaneous reporting indicates a signal for QT prolongation and the potential for underreporting is recognised.

On the basis of the available data, the PhVWP considered that it is not possible to conclude that there is a substantially lower risk for QT-prolongation with escitalopram than with citalopram, and therefore, the same risk minimisation measures should apply. In considering the appropriate risk minimisation strategy, the PhVWP also noted that elderly patients achieve higher systemic exposure than younger patients.

The new recommendations are as follows:

- In the elderly (> 65 years of age), the recommended maximum dose of **escitalopram** is now reduced to 10 mg daily.
- The maximum dose of **escitalopram** for adults ≤ 65 years remains 20 mg daily.

Patients treated with citalopram or escitalopram should be advised to contact a healthcare professional immediately if they experience symptoms of an abnormal heart rate or rhythm while taking these medicines. Patients should not stop taking citalopram or escitalopram or change or reduce the dose without first consulting their healthcare professional, as withdrawal symptoms may occur, especially if discontinued abruptly(as above, please refer to the product information for advice regarding withdrawal symptoms). Healthcare professionals are advised to review elderly patients who currently take doses that are above the new recommended maximum dose, and gradually reduce the dose accordingly. Cases of QT interval prolongation have been reported also in association with other SSRIs. For further information, please refer to the respective product information.

This information was recently communicated to Healthcare Professionals by the marketing authorisation holder, in agreement with the IMB. DHPCs are available on **www.imb.ie**).

Suspected adverse reactions associated with the use of citalopram or escitalopram, particularly cardiac disorders, should be reported to the IMB via the usual routes.

Key Message:
Citalopram and escitalopram are associated with dose-dependent QT interval prolongation. Risk minimisation measures will be implemented including new contraindications and warnings and dosing recommendations.

Strattera (atomoxetine) – Effects on blood pressure and heart rate

Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD.

A new analysis requested by the PhVWP showed that approximately 6-12% of children and adults with ADHD (attention deficit hyperactivity disorder) treated with Strattera experienced clinically relevant changes in heart rate (20 bpm or greater) and/or blood pressure (15-20 mmHg or greater). The absolute number of patients with these types of changes was small but since in approximately 15-32% of them these changes were sustained or persistent, the PhVWP recommended a series of measures to minimise any risk of cardiovascular adverse effect. These measures include a recommendation for pre-treatment screening and periodic cardiovascular monitoring during treatment, and a contraindication for the use of Strattera in patients with severe cardiovascular or cerebrovascular disorders.

Advice to Healthcare Professionals:

- Strattera can affect heart rate and blood pressure.
- Strattera should not be used in patients with severe cardiovascular or cerebrovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate).
- Strattera should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.
- It is recommended that patients who are being considered for treatment with Strattera should have a careful history and physical examination to assess for the presence of cardiac disease. Patients should be referred for specialist cardiac evaluation if initial findings suggest such history or presence of cardiac disease.
- Heart rate and blood pressure should be measured and recorded (e.g. on a centile chart) in all patients before treatment with Strattera is started as well as after each adjustment of dose and then at least every 6 months during treatment to detect possible clinically important increases. If patients develop symptoms suggestive of cardiac disease during treatment they should be referred for prompt specialist cardiac evaluation.

The magnitude of the increase in blood pressure and heart rate could be a potential risk in patients with severe cardiovascular or cerebrovascular disorders. Some examples of patients who would be expected to experience critical deterioration in their preexisting condition would include those with the following conditions: severe hypertension, advanced heart failure or arterial occlusive disease, progressive unstable angina, haemodynamically significant congenital heart disease or cardiomyopathies, recent or repeated myocardial infarction, and potentially life-threatening arrhythmias, channelopathies (disorders caused by the dysfunction of ion channels), cerebral aneurysm and stroke.

Key Message
Strattera can cause clinically important changes in blood pressure and/or heart rate in some patients. New risk minimisation measures include pre-treatment screening and periodic cardiovascular monitoring during treatment, and a contraindication for the use of Strattera in patients with severe cardiovascular or cerebrovascular disorders.

Pradaxa (dabigatran etexilate) – Recommendations for assessment of renal function and monitoring in the elderly

Pradaxa is a potent, competitive, reversible direct thrombin inhibitor, which was authorised through an EU assessment procedure and is currently licensed for use in the following indications:

- Primary prevention of venous thromboembolic events in adults who have had elective total hip replacement or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors (see Summary of Product Characteristics (SPC), available on **www.ema.europa.eu**).

Following a recent EU evaluation of all available safety data on the risk of fatal haemorrhage, new recommendations to assess renal function prior to and during treatment with Pradaxa were introduced as follows:

- **Prior to initiation of treatment with Pradaxa, renal function should be assessed in all patients by calculating creatinine clearance (CrCl) to exclude treatment in patients with severe renal impairment (i.e. CrCl < 30 ml/min).**
- **While on treatment, renal function should be assessed in clinical situations where a decline in renal function is suspected or where renal function could deteriorate (e.g. hypovolemia, dehydration, and with certain co-medications).**
- **In elderly patients (> 75 years), or in patients with renal impairment, renal function should be assessed at least once a year.**
- **Pradaxa is contraindicated in patients with severe renal impairment.**

The EU evaluation was initiated following reports of fatal cases of haemorrhage in Japan. The review indicated that most patients that experienced fatal haemorrhage were elderly and had severe renal impairment. As with other anticoagulants, haemorrhage is a well known adverse reaction with Pradaxa and advice on this risk is already reflected in the product information, which recommends that doctors check for signs of bleeding and discontinue treatment in patients with severe bleeding. It also recommends that an unexplained fall in haemoglobin and/or haematocrit, or blood pressure should lead to a search for a bleeding site.

Pradaxa is contraindicated in patients who are bleeding, in patients with severe renal impairment, and should be used with caution and at lower doses in elderly patients and patients with moderate renal impairment. Patients at increased risk of bleeding should be closely clinically monitored for signs of bleeding and anaemia. The SPC advises that the following factors increase the risk of bleeding associated with Pradaxa (see SPC for full details):

- age >75 years
- moderate renal impairment (30-50 ml/min CrCL)
- low body weight
- use of acetylsalicylic acid, clopidogrel or NSAIDs
- presence of oesophagitis/gastritis/gastroesophageal reflux requiring treatment
- strong P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil)

Any suspected adverse reactions associated with the use of Pradaxa should be reported to the IMB via the usual reporting routes (see **www.imb.ie** for details).

This information was recently communicated to Healthcare Professionals by the marketing authorisation holder in agreement with the IMB (DHPC is available on **www.imb.ie**).

Key Message:
Renal function should be assessed in all patients prior to initiating treatment with Pradaxa.

While on treatment, renal function should be assessed in clinical situations where a decline in renal function is suspected.

In elderly patients (> 75 years) or in patients with renal impairment, renal function should be assessed at least once a year. As serum creatinine values alone are often insufficient to accurately evaluate renal function, creatinine clearance should be assessed to ensure that such patients do not have renal impairment that precludes the safe and effective use of Pradaxa (i.e. CrCl < 30 mL/min).

Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

Product	Safety Issue
Pradaxa (dabigatran etexilate)	Recommendations for monitoring renal function in the elderly
Cipramil (citalopram)	Association with dose-dependent QT interval prolongation
Lexapro (escitalopram)	Association with dose-dependent QT interval prolongation
Revlimid (lenalidomide)	Risk of second primary malignancies