IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

61ST EDITION

Domperidone-containing medicines: risk of cardiac adverse reactions-restricted indication, new contraindications and reduced dose and duration of use

A recent Europe-wide review has recommended updates to the treatment advice for domperidone containing medicines following an evaluation of the benefits and risks of domperidone. This review was triggered following continued receipt of reports of cardiac adverse reactions, with a small increase in the risk of serious cardiac effects confirmed. A higher risk was observed in patients older than 60 years, in adults taking daily oral doses of more than 30mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly.

The review concluded that domperidone is associated with a small increased risk of serious cardiac adverse reactions. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced. Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors.

These recommendations are based on an evaluation of the available evidence of safety and efficacy of domperidone from various sources. This comprised of non clinical and clinical data, both published and unpublished, including a Thorough QT (TQT) study, a cumulative review of case reports of cardiac disorders and vascular investigations from the safety databases for domperidone containing products and pharmacoepidemiological studies. Overall there was sufficient evidence to support the use of oral domperidone 10 mg up to three times a day in the relief of nausea and vomiting in adults. There were limited data to support paediatric use in this indication, and although the mechanism of action is not expected to differ between adults and children, studies to provide further data to support efficacy in the paediatric population have been requested. Data in support of other indications were extremely limited. In particular, there was little evidence in support of the long-term efficacy of domperidone in dyspepsia and gastro-oesophageal reflux disorder. The benefits in these indications were therefore not considered to outweigh the risk.

Although the results of the TQT study with domperidone indicate that it does not significantly prolong the QTc interval when administered to healthy subjects at 10 mg and 20 mg four times daily, there are limitations in the study that restrict the conclusions that can be drawn. Epidemiological studies mostly suggest that domperidone exposure was associated with an increase in risk for sudden cardiac death or ventricular arrhythmia. Some of these studies also supported a greater risk in patients over 60 years of age or who were taking high doses (over 30 mg/day).

Advice to Healthcare Professionals

Restricted indication

- The use of domperidone is now restricted to the relief of symptoms of nausea and vomiting. The available evidence of efficacy was not sufficient to support its use for other indications.

New contraindications

Domperidone is now contraindicated in people with:

- conditions where cardiac conduction is, or could be, impaired,
- in those with underlying cardiac diseases such as congestive heart failure,
- in those receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors, and
- in people with severe hepatic impairment.

In this edition

Restrictions on dose

The dosage and duration of use have been reduced to mitigate the risk of cardiac adverse reactions as follows:

Oral formulations

- For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day).
- In children under 12 years of age and weighing less than 35kg, the recommended maximum dose in 24 hours is 0.75mg/kg body weight (dose interval: 0.25mg/kg body weight up to three times a day).
- In order to accurately measure doses to paediatric patients, oral suspensions should be given using an adapted graduated oral syringe.

Suppository formulation

- Suppositories should only be used in adults and adolescents weighing 35kg or more, the recommended maximum daily dose in 24 hours is 60mg (dose interval: 30mg twice a day).

Duration of treatment

- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- The maximum treatment duration should not usually exceed one week.
- Patients currently receiving long-term treatment with domperidone should be reassessed at a routine appointment to advise on treatment continuation, dose change, or cessation.

Key Message

- **Domperidone is associated with a small increased risk of serious cardiac adverse reactions. Use of domperidone is now restricted to the relief of symptoms of nausea and vomiting. It should no longer be used for the relief of bloating and heartburn.**
- **The dosage and duration of use have been reduced. It should be used at the lowest effective dose for the shortest duration possible. The maximum treatment period should not usually exceed one week.**
- **Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors.**

* **Products currently authorised in Ireland include Motilium and Domerid. Further details are available at www.imb.ie**

Recommendation to restrict the combined use of medicines affecting the renin-angiotensin (RAS) system

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risks of combining different classes of medicines that act on the renin-angiotensin (RAS) system. These medicines, which are called RAS-acting agents, belong to three classes:

1. Angiotensin-receptor blockers (ARBs) for example candesartan, telmisartan, valsartan, losartan, olmesartan and irbesartan,*
2. Angiotensin-converting enzyme inhibitors (ACE inhibitors) for example captopril, enalapril, lisinopril, ramipril, perindopril and zofenopril,*
3. Direct renin inhibitors such as aliskiren,* which is the only authorised substance in its class.

The PRAC has advised that combining medicines from any two of these classes should not be recommended, and in particular that patients with diabetic nephropathy should not be given an ARB with an ACE-inhibitor. Where such a combination (known as dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, electrolyte balance and blood pressure. This recommendation also extends to the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in patients with renal impairment or diabetes mellitus.

The benefit-risk of the individual RAS-acting agents used as monotherapy or as combination therapy with antihypertensive agents from other classes such as beta blockers were not considered within the scope of this PRAC review and any issues identified applied only to dual RAS blockade therapy.

The PRAC reviewed the totality of the available data, including clinical trials, meta-analysis and publications. It was of the opinion that there is considerable evidence from these, in particular the Makani et al meta-analysis,[1] ONTARGET (Yusuf et al. 2008),[2] ALTITUDE (Parving et al. 2012)[3] and the prematurely terminated VA NEPHRON-D trial (the VA NEPHRON-D Investigators, 2013),[4] which demonstrate that dual RAS blockade through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with an increased risk of adverse events, including hypotension, hyperkaleamia and renal failure compared to monotherapy. The Makani et al meta-analysis reinforces conclusions from individual studies, that the likely benefits from dual blockade are limited to a reduction in hospital

admissions for heart failure among people with pre-existing heart failure, and highlights some important safety concerns associated with dual therapy. Based on the totality of the evidence, the PRAC has recommended that dual therapy should be restricted to limited situations under specialist supervision after careful consideration of the likely risks and benefits.

Following this EU level review, there will be harmonised implementation of these recommendations into product information in order to reflect the available information and adequately manage the concerns identified with regards to dual RAS blockade therapy and the overall conclusion that dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment e.g. in a selected group of symptomatic patients with heart failure and reduced left ventricular function in whom other treatments are unsuitable.

Section 4.4 of the Summary of Product Characteristics (SmPC) will be updated for all products accordingly to highlight that dual RAS blockade through the combined use of ACE-inhibitors, ARBs or aliskiren is not recommended and if, considered absolutely necessary, should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. It will be clearly specified however that ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Advice to Healthcare Professionals

- The benefit risk balance of RAS-acting agents remains favourable when used in line with the updated recommendations.
- Dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment-e.g. in a selected group of symptomatic patients with heart failure and reduced left ventricular function in whom other treatments are unsuitable.
- The combined use of ACE-inhibitors, ARBs or aliskiren increases the risk of adverse events such as hyperkalaemia, hypotension and renal impairment compared to use of these medicines alone.
- Dual blockade of the RAS system is therefore generally not recommended and should not be used in patients with diabetic nephropathy.
    - If dual RAS blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
- In patients with diabetes mellitus or renal impairment (GFR < 60ml/min), the concomitant use of ACE inhibitors or ARBs with aliskiren-containing products is contraindicated.

Key Message

Dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment such as in a selected group of symptomatic patients with heart failure and reduced left ventricular function with the necessary monitoring and specialist supervision. Combined use of ACE inhibitors, ARBs or aliskiren is associated with an increased risk of adverse events, including hypotension, hyperkalaemia and renal failure compared to monotherapy.

* Products currently authorised in Ireland include Atacand, Blopress (candesartan), Micardis (telmisartan) Diovan (valsartan), Co-Diovan (valsartan and hydrochlorothiazide) Cozaar (losartan), Approvel (irbesartan), Omesar (olmesartan), Omesar Plus (olmesartan and hydrochlorothiazide), Konverge (olmesartan and amlodipine), Konverge Plus (olmesartan, amlodipine, hydrochlorothiazide), Captor (captopril), Innovace (enalapril), Zestril (lisinopril),Zestoretic (lisinopril and hydrochlorothiazide) Zofenil (zofenopril), Tritace (ramipril), Coversyl (perindopril) and Rasilez (aliskiren), Rasilez HCT (aliskiren and hydrochlorothiazide), Rasilamlo (aliskiren and amlodipine). Generics of some products are also available. Further details are available at www.imb.ie

References

1. Makani H, et al. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013; 346: f360.
2. Yusuf s, et al. Telmisatran, ramilpril or both in patients at high risk for vascular events. N Engl J Med 2008; 358:1547-59.
3. Hans-Henrik Parving, et al. Cadiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012; 367:2204-2213.
4. VA Nephron-D Investigators. Combined Angiotensin Inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013; 369:1892-1903.

Reminder regarding the risk of serious hypersensitivity reactions with Rienso (ferumoxytol)

Parenterally administered iron preparations are known to cause hypersensitivity reactions including serious and potentially fatal anaphylactic reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

Rienso (containing iron as ferumoxytol) was authorised for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD) in June 2012 and was therefore not included in the previous EU review of other parenteral iron containing products which started in December 2011 and whose outcome was communicated via a Dear Healthcare Professional Communication (DHPC) and in the 58th edition of the IMB Drug Safety Newsletter (DSN). However Rienso's Product Information has been aligned with that of all the other IV irons.

During post marketing use of Rienso, serious hypersensitivity reactions including anaphylactic reactions, some of which have been life-threatening or fatal, have been reported in patients receiving Rienso. The benefits and risks of Rienso are currently being evaluated in the context of a regular procedure known as Periodic Safety Update Report (PSUR). A PSUR is intended to re-evaluate the benefit risk ratio of a medicinal product at defined time points post-authorisation. Whilst the finalisation of this assessment is awaited, healthcare professionals are reminded of the following advice:

Advice to Healthcare Professionals

- Rienso is contraindicated in patients with known serious hypersensitivity to other parenteral iron products.
- The risk of hypersensitivity is increased in patients with known allergies (including drug allergies), in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy. In these patients, Rienso should only be used if the benefit is clearly judged to outweigh the potential risk.
- Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions as well as resuscitation facilities are immediately available.
- Patients should be closely monitored for signs of hypersensitivity including severe hypotension during and for at least 30 minutes after each administration of Rienso.
- Before each administration patients should be informed of the risk of hypersensitivity. Patients should also be informed of the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.

Key Message
Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions as well as when resuscitation facilities are immediately available.

Further details on Rienso are available at www.imb.ie.

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

Product	Safety Issue
Domperidone-containing medicines	Domperidone:new recommendations to minimise the cardiac risks
Fastum Gel (ketoprofen)	Risk minimisation measures for ketoprofen-containing topical formulations.

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