IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

57TH EDITION

Ondansetron for intravenous use – updated information on posology to mitigate dose-dependent risk of QT interval prolongation

Ondansetron* is a selective 5-HT3 receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of post operative nausea and vomiting.

Prolongation of QTc interval and cardiac arrhythmia, including Torsade de Pointes, are known risks with ondansetron. The IMB previously highlighted the new maximum single dose of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in adults in the 49th edition of the IMB Drug Safety Newsletter (DSN) published in August 2012. This restriction, followed a review of study data, which showed that there is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for CINV. Prolongation of the QTc interval can lead to Torsade de Pointes (TdP), a potentially life-threatening cardiac arrhythmia.

Further analyses of the study data and data from other sources has lead to new recommendations for repeat dosing in all adults, dosing for prevention of CINV in the elderly and dilution and administration for prevention of CINV for patients aged 65 years or older. This information will be communicated to healthcare professionals by the innovator marketing authorisation holder in conjunction with the IMB and will be available on www.imb.ie.

New Advice to Healthcare Professionals

- Elderly patients aged 75 years or older: A single dose of intravenous ondansetron given for the prevention of CINV must not exceed 8mg (infused over at least 15 minutes).
- Adult patients aged less than 75 years: A single dose of intravenous ondansetron given for the prevention of CINV in adults (aged less than 75 years) must not exceed 16mg (infused over at least 15 minutes).
- Repeat dosing in all adult patients (including elderly patients): Repeat intravenous doses of ondansetron for the prevention of CINV should be given no less than 4 hours apart.
- Dilution and administration in elderly patients aged 65 years or older: All intravenous doses of ondansetron for the prevention of CINV should be diluted in 50-100mL saline or other compatible fluid infused over at least 15 minutes.

Reminder of Previous Advice to Healthcare Professionals

- Ondansetron should be avoided in patients with congenital long QT syndrome.
- Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- Caution should be exercised if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. Risk factors include patients with:
  - electrolyte abnormalities,
  - congestive heart failure,
  - bradyarrhythmias,
  - use of other medicines that prolong the QT interval (including cytotoxic drugs), or medicines that may lead to electrolyte abnormalities,
  - use of medicines which lower heart rate.

There are no changes to the recommendations currently included in the product information for:

- Oral and rectal dosing for CINV in adult patients (including elderly patients).
- IV or oral dosing for the prevention and treatment of post-operative nausea and vomiting in adult patients.
- IV or oral dosing for any indication in the paediatric population.

In this edition

Key Message

- The new maximum single intravenous dose of ondansetron for the management of CINV in adults aged 75 years and older is now 8mg (infused over at least 15 minutes).
- The new maximum single intravenous dose of ondansetron for the management of CINV in adults aged less than 75 years old is now 16mg (infused over at least 15 minutes).
- Repeat dosing in all adults for the prevention of CINV should happen no less than 4 hours apart.
- All intravenous doses of ondansetron for CINV should be diluted in 50-100 mL of saline or other compatible fluid and infused over at least 15 minutes.

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

Agomelatine (Valdoxan)–New contraindication and a reminder of the importance of liver function monitoring

Agomelatine* is a melatonergic agonist, indicated in the treatment of major depressive episodes in adults, which has been authorised for use across the EU since February 2009. Agomelatine exerts its pharmacological effect by agonist activity at the melatonin MT1 and MT2 receptors, and antagonism at the serotonin 5-HT2C receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

A risk of hepatic adverse effects has been known to be associated with agomelatine since it was first authorised and the product information has included warnings about these risks and the requirement for regular monitoring of liver function tests during treatment with agomelatine. Since then, cases of liver injury, including hepatic failure, elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine. The majority of these abnormalities occurred during the first months of treatment and the pattern of liver damage appears mainly hepatocellular. When agomelatine was discontinued, the serum transaminases usually returned to normal levels. In December 2012, the IMB highlighted the risk of hepatotoxicity in its Drug Safety Newsletter (51st edition) and emphasised the importance of liver function monitoring.

As further cases of severe hepatic adverse reactions have been reported the product information is being further updated to contraindicate the use of agomelatine in patients with transaminases exceeding three times the upper limit of normal. Prescribers are again reminded of the existing warnings and the need for liver function monitoring.

Prescribers should also be aware of updates to the product information concerning use in the elderly. Whilst the efficacy and safety of agomelatine (25-50 mg/day) have been established in patients < 75 years, no significant effect has been identified in patients 75 years or older. Therefore, considering the lack of significant benefit in very elderly patients (≥75 years) and the vulnerability of this age group, agomelatine should not be used in patients aged 75 years or older.

Advice for Healthcare Professionals

- Do not prescribe agomelatine in the following situations
  - in patients with hepatic impairment i.e. cirrhosis or active liver disease,
  - in patients with transaminases exceeding 3 times the upper limit of normal,
  - in patients aged 75 years and over (no significant benefit has been documented in this group).
- Caution should be exercised when prescribing agomelatine for patients with risk factors for hepatic injury e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, substantial alcohol intake or use of concomitant medicines associated with risk of hepatic injury.
- Liver function tests (LFTs) should be monitored in all patients receiving agomelatine as follows and agomelatine treatment should be discontinued if a patient presents with symptoms or signs of liver injury:
  - at initiation of treatment,
  - periodically at 3 weeks, 6 weeks (end of acute phase), 12 weeks, 24 weeks (end of maintenance phase) and thereafter, when increasing the dose of agomelatine at the same time intervals that apply to initiation of treatment,
  - whenever clinically indicated.
- Any patient who develops increased serum transaminases should have their LFTs repeated within 48 hours.
- Patients should be informed of the symptoms of potential liver injury, and should be advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.
- Any suspected adverse reactions associated with use of agomelatine should continue to be reported to the IMB in the usual way.

Key Message

- Cases of liver injury, including hepatic failure resulting in fatal outcome or liver transplantation in patients with hepatic risk factors, have been reported in association with post-marketing use of agomelatine.
- Agomelatine is contraindicated in patients with transaminases exceeding 3 times the upper limit of normal.
- LFTs should be monitored in all patients during treatment, in line with the recommendations.
- Patients should be informed of the symptoms of liver injury and the need for immediate follow up with a healthcare professional if these symptoms appear.

* Product information for agomelatine is available at www.imb.ie

Restrictions to the use of Short Acting Beta Agonists (SABAs) in obstetric indications

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended restricting the use of Short Acting Beta Agonists (SABAs) in obstetric indications. It was recommended that these agents no longer be used in oral or suppository forms in obstetric indications, such as for suppressing premature labour or excessive labour contractions. However, PRAC has recommended that injectable forms of these medicines should remain authorised for short-term obstetric use under specific conditions. In Ireland, only injectable forms of these medicines* are licensed for use in obstetric indications.

Given the known risk for cardiovascular adverse effects (such as tachycardia and arrhythmia) with high doses of SABAs, the medicines used in obstetric indications already carry safety warnings in their prescribing information and must not be used in patients with a history of, or a risk for cardiovascular disease. The PRAC assessed the available data from clinical studies, post marketing reports, and the published literature and considered the relevant treatment guidelines. The review concluded there was a risk for serious cardiovascular adverse effects for both the mother and unborn baby when SABAs are used in obstetric indications, with the data suggesting these mostly occur with prolonged use. No statistically significant effect of tocolysis on perinatal mortality or morbidity has been observed in randomised, controlled trials. SABAs are associated with serious and dose dependent adverse events, predominantly cardiovascular, observed in both the mother and foetus. It was considered that there is insufficient evidence to support the use of prophylactic oral betamimetics for preventing preterm birth in women at high risk of preterm labour with a singleton or twin pregnancy. Given the cardiovascular risks and the very limited data of supporting the benefits of SABAs used via the oral or rectal route as short or longer term tocolytics, the PRAC concluded that their risks were greater than the benefits in obstetric indications and therefore should no longer be used.

Parenteral SABAs are efficacious in the rapid relaxation of the uterus. Women most likely to benefit from the use of tocolytic drugs are those who are at very preterm labour. The delay in preterm labour achieved may be used to implement other measures known to improve perinatal health. Similarly, the use of SABAs in emergency conditions and to enable external cephalic version (ECV) is supported as this reflects limited duration of use, and minimal dosing. On the basis of the evidence evaluated, PRAC has concluded that the benefits of parenteral SABA formulations exceeds the risks in the obstetric indication of tocolysis in the short-term only, limited to a maximum of 48 hours for patients between 22 and 37 weeks of gestation and under specialist supervision. In order to minimise and manage risk to mothers and the foetus, PRAC also recommended that use in tocolysis should be subject to appropriate pre-treatment screening and patient monitoring in order to identify the early onset of cardiovascular events and further minimise risk of a serious cardiovascular event.

Advice to Healthcare Professionals

- The use of parenteral SABAs should be limited to 48 hours maximum and should be administered under specialist supervision in all authorised obstetric indications (see product information).
- SABAs are associated with serious, sometimes fatal, adverse cardiovascular events in both the mother and the foetus/newborn.
- Parenteral SABAs should not be used in women with a history of heart disease or in conditions where prolongation of the pregnancy is hazardous to the mother or foetus.

Key Message

- Due to the risk of cardiovascular events in both the mother and the foetus, parenteral SABAs should be limited to short term use (up to 48 hours) and used under specialist supervision in all authorised obstetric indications.
- Parenteral SABAs should not be used in women with a history of heart disease or in conditions where prolongation of the pregnancy is hazardous to the mother or foetus.

* Parenteral SABAs authorised for the management of tocolysis in Ireland are Ventolin 500mcg/ml solution for injection, Ventolin 1mg/ml Concentrate for Solution for intravenous infusion and Bricanyl 500mcg/ml solution for injection or infusion. Further details are available at www.imb.ie.

Trazodone–Reminder of the risk of postural hypotension and somnolence in the elderly particularly in the context of polypharmacy

Trazodone* is an antidepressant authorised in Ireland for the relief of symptoms in depression including depression accompanied by anxiety. It is a triazolopyridine derivative, chemically unrelated to known tricyclic, tetracyclic and other antidepressant agents. At low sub-therapeutic doses, trazodone acts as a 5-HT antagonist while at higher doses it inhibits 5-HT reuptake. It is also a weak inhibitor of noradrenaline re-uptake.

In response to information from case reports, the available evidence on the known risks of postural hypotension and somnolence with trazadone was recently reviewed at EU level. This review confirmed that such adverse events may occur more often in elderly patients particularly with concomitant use of other potentially sedative or antihypertensive.

Careful consideration should be given to the potential for the additive effects of concomitant medication such as with potentially sedative or antihypertensives, or in the presence of risk factors such as co-morbid disease, which may exacerbate these reactions. It is recommended that the patient/carer is informed of the potential for these reactions with appropriate monitoring for such effects following initiation of therapy, prior to and following upward dose titration. For very elderly or frail patients, the recommended initial dose is reduced to 100 mg a day, administered in divided doses or as a single night time dose. This may be incrementally increased under supervision, according to tolerance and efficacy. In general, single doses above 100 mg should be avoided in these patients. The product information has been strengthened to highlight the risk of potential additive effects of concomitant medication and the possible impact of co-morbid conditions.

Key Message

- Elderly patients may more often experience orthostatic hypotension, somnolence and other anticholinergic effects of trazodone.
- Careful consideration should be given to the potential for additive effects with concomitant medication such as with other psychotropics or antihypertensives or in the presence of risk factors such as comorbid disease.
- There should be particular awareness of the potential for such effects following initiation of therapy, prior to and following upward dose titration.

* Products available in Ireland include Molipaxin. Further details are available at www.imb.ie

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

Product	Safety Issue
Efient (prasugrel)	Increased risk of serious bleeding in unstable angina/NSTEMI patients when EFIENT is administered prior to diagnostic coronary angiography.
Pixuvri (pixantrone)	Communciation on the risk of dosing error with Pixuri (pixantrone).
Gilenya (fingolimod)	Haemophagocytic syndrome reported in patients treated with Gilenya (fingolimod).
Intravenous Iron products	Strengthened recommendations regarding the risk of serious hypersensitivity reactions with intravenous iron products.
Hydroxyethyl Starch (HES)	Restriction of use of hydroxyethyl starch (HES) products.
MabThera (rituximab)	Recommendation to screen for hepatitis B virus before treatment with MabThera (rituximab).
Jevtana (cabazitaxel)	Communication regarding the potential for medication error in the preparation of Jevtana (cabazitaxel).
Erivedge (vismodegib)	Important information to support safe use, including a pregnancy prevention programme.