IRISH MEDICINES BOARD

ONDANSETRON-UPDATED INFORMATION ON POSOLOGY TO MITIGATE DOSE-DEPENDENT RISK OF QT INTERVAL PROLONGATION

Ondansetron* is a selective $5HT_3$ receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and also for the prevention and treatment of post operative nausea and vomiting.

Prolongation of QTc interval and cardiac arrhythmia, including Torsade de Pointes (TdP), 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 and in the October 2012 edition of MIMS Ireland. 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 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 patients aged 75 years of older, and dilution and administration for prevention of CINV in patients aged 65 years or older. This information was recently communicated to healthcare professionals by the Innovator marketing authorisation holder in conjunction with the IMB and is 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 patient):* 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 used 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.

Key message

- The new maximum single dose 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 ondansetron doses for CINV should be diluted in 50-100 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*