There are three NOACs licensed for use in Ireland and across the EU, the direct thrombin inhibitor, dabigatran and the two direct factor Xa inhibitors, rivaroxaban and apixaban*. Clinical trials and post-marketing experience have shown that major bleeding events, including events leading to death, are not confined to vitamin K antagonists/LMWH but are also significant risks for these NOACs. Furthermore, analysis of EU post marketing reports suggests that not all prescribers in the EU are sufficiently aware of the advice in the product information for the novel agents in terms of managing bleeding risks.


In light of the risk of haemorrhage for all anticoagulants, prescribers should consider each individual patient's risk of bleeding and observe posology recommendations, contraindications and warnings and precautions for use to minimise the risk of bleeding. This includes a careful benefit-risk assessment in patients with lesions, conditions, procedures and/or treatment (e.g. NSAIDs and antplatelets) which increase the risk of major bleeding. In addition, clinical surveillance for signs and symptoms of bleeding is recommended throughout the treatment period especially in patients at increased risk of bleeding. While differences in contraindications exist between the NOACs, they share the following contraindications:

- Active clinically significant bleeding.
- Significant risk factors for major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives, oral anticoagulants (warfarin etc) except under the circumstances of switching to or from the medicine, or when unfractionated heparin is given at doses to maintain an open central venous or arterial catheter.

Information regarding additional contraindications specific to each NOAC is described in the product information (Summary of Product Characteristics (SmPC) and Package leaflet (PL)) for each individual medicine available at www.imb.ie.
There is currently no specific antidote available for NOACs and the product information for each product includes advice on treatment in the event of bleeding complications.

Attention should also be paid to renal function. Renal impairment may constitute a contraindication or a reason to consider not using the medicines or reducing the dose. Please refer to the product information since recommendations differ between the three medicines.

National Monitoring Experience

The majority of reports of suspected adverse reactions associated with the use of NOACs have been consistent with the expected effects mainly involving various types of haemorrhagic effects ranging from contusions, haematoma and wound secretions to gastrointestinal haemorrhage and menorrhagia. There have also been some reports of DVT, pulmonary embolism and cardiac effects, which would not be unexpected in the patient population. For those cases for which information on outcome is available, the majority of patients were reported to have recovered. The IMB and EMA will continue to monitor experience with use of these NOACs and will highlight relevant, new information which becomes available, as appropriate. Healthcare professionals should continue to report any adverse reactions suspected to be associated with the use of NOACs to the IMB using an Adverse Reaction Report Form (Yellow Card) obtained either from the IMB or electronically via the website at www.imb.ie. Alternatively they may be reported by telephone (01 676 4971) or fax (01 676 2517).

Key Message

- Close clinical surveillance, including monitoring for signs of haemorrhage, to facilitate early intervention and management is recommended for all patients treated with NOACs.
- Detailed, product specific information and advice to support safe and appropriate use of NOACs is provided in the individual SmPCs and educational materials for each of the products.
- Renal function should be assessed and monitored during treatment in line with the recommendations in the product information.
- Patients and caregivers should be advised about the risk of bleeding complications associated with NOACs and of the importance of carrying their patient alert cards at all times.

* See product information for each individual product for details on licensed indications available at www.imb.ie

Metoclopramide-containing medicines – Update on outcome of review and revised recommendations for use

Metoclopramide* is an antiemetic, which has been authorised for many years for the treatment of a number of gastrointestinal disorders, including nausea and vomiting associated with chemotherapy, radiotherapy and migraine, following surgery and in the management of gastrointestinal motility disorders.


An EU review of the benefits and risks associated with use of metoclopramide-containing medicines was recently completed, which included evaluation of data from published studies, meta-analyses on efficacy and analysis of reports of suspected adverse reactions. This review was initiated following concerns related to the efficacy of metoclopramide, as well as the risks of neurological and cardiovascular toxicity.

The review confirmed the well known risks of neurological effects such as acute extrapyramidal disorders, involuntary movement disorders and tardive dyskinesia. The risk of acute neurological effects is higher in children, although tardive dyskinesia was reported more frequently in the elderly. An increased risk of these adverse effects was also associated with high dose or long term treatment. The evidence indicated that these risks outweigh any benefits of using metoclopramide for the treatment of chronic conditions. As a result of this review, a number of changes to restrict the indications, dose and duration of use of metoclopramide-containing medicines have been recommended and a Direct Healthcare Professional Communication (DHPC) will be circulated and published on the IMB website (www.imb.ie). The product information will be updated accordingly also.

Advice to Healthcare professionals

- In order to minimise the risks of neurological and other adverse reactions, metoclopramide should only be prescribed for short-term use (up to 5 days). It should no longer be used in chronic conditions such as gastroparesis, dyspepsia and gastro-oesophageal reflux disease, nor as an adjunct in surgical and radiological procedures.
- In adults, metoclopramide remains indicated for prevention of post-operative nausea and vomiting (PONV), radiotherapy-induced nausea
and vomiting and delayed (but not acute) chemotherapy-induced nausea and vomiting, and for symptomatic treatment of nausea and vomiting including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).

- In children, metoclopramide should only be used as a second-line option for delayed chemotherapy induced nausea and vomiting and treatment of established PONV. Use is contraindicated in children less than 1 years of age.

- For adults and children the maximum dose in 24 hours is 0.5 mg per kg body weight; in adults, the usual dose of conventional formulations (all routes) is 10 mg up to three times daily. In children the recommended dose is 0.1 to 0.15 mg per kg body weight, repeated up to three times daily.

- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.

- Rare reports of serious cardiovascular reactions, associated with metoclopramide, particularly via the intravenous route, have been reported. Therefore special care should be taken in at risk populations including the elderly, patients with cardiac conduction disturbances, uncorrected electrolyte imbalance or bradycardia, and those taking other drugs known to prolong QT interval.

- Patients currently taking regular metoclopramide should have their treatment reviewed at a routine medical appointment.

- Because of the risk of adverse reactions with high doses, some high-strength formulations of metoclopramide products will be withdrawn.

- The product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) will be updated accordingly in due course.

Key Message

- Metoclopramide is now indicated for short-term use in adults in the prevention and treatment of nausea and vomiting, including that associated with chemotherapy, radiotherapy, surgery and migraine.

- Metoclopramide should only be prescribed for short-term use (up to 5 days) only, at recommended dose and dose-intervals.

- Intravenous doses should be administered as a slow bolus (at least over 3 minutes) to minimise the risk of occurrence of adverse reactions, including cardiovascular reactions.

- Intravenous metoclopramide is only indicated for the second line treatment of postoperative nausea and vomiting in children from 1 year of age. For adults and children, the maximum dose is 0.5 mg per kg body weight in 24 hours.

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

Reminder regarding changed arrangements for Drug Safety Newsletter (DSN) Distribution

Further to previous updates regarding revised arrangements for electronic distribution of the DSN (Edition 53 published in May 2013
http://www.imb.ie/images/uploaded/documents/Drugs20Safety%20Newsletter%2053%20(web)%20hyperlinked%20version%20final.pdf), from early 2014, hard copy versions of the DSN will no longer be printed and posted. The IMB is therefore continuing to collate and prepare distribution lists to facilitate this process. A number of readers have already provided their email contact details or have registered to receive email alerts when a new edition of the DSN has been published.

For readers who have not yet provided their email contact details to receive the electronic version of the DSN or registered to receive alerts, please do so at your earliest convenience to allow you to continue to receive the DSN. Please note that healthcare professionals operating from more than one centre are welcome to submit email addresses for more than one location.

To ensure you can continue to receive all issues of the DSN, please register on the IMB website (www.imb.ie) to receive an alert when a new issue is published, or alternatively, submit your email address (or email addresses), details of your profession (i.e. doctor (G.P./hospital doctor), pharmacist (community/hospital), nurse, dentist etc.) and the postal address where you have been receiving a hard copy of the DSN (if relevant) to imbpandpharmacovigilance@imb.ie, to allow an electronic version to be emailed directly to you and to facilitate reconciliation with the postal mail list.

Registration on the IMB website also allows you to receive other information/alerts issued by the IMB.
Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

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