HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Oral Anticoagulants
Update on National Monitoring Experience

Oral anticoagulants are used for managing thromboembolic complications in conditions such as primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery, prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, treatment of and prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism in adults and prevention of atherothrombotic events in adult patients after acute coronary syndrome (ACS). While there are some common indications and contraindications for use of these medicines, there are also a number of differences. As such, it is important to regularly check the full details of the licensed indications, contraindications, precautions and warnings for the individual oral anticoagulants, which are described in detail in the product information (Summary of Product Characteristics (SmPC) and Package leaflet (PL)) for each of these medicines. These documents are accessible from www.hpra.ie.

The older oral anticoagulants, such as warfarin, are vitamin K antagonists. The newer oral anticoagulants, apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto) collectively known as 'NOACs' exert their effects through inhibition of factor Xa or of thrombin. Apixiban and rivaroxaban inhibit factor Xa (activated factor X). Factor Xa is involved in the conversion of prothrombin to thrombin. Thrombin is involved in the conversion of fibrinogen to fibrin which then leads to formation of a fibrin clot. Dabigatran inhibits thrombin. It is given as the prodrug dabigatran etexilate, which is converted to dabigatran in the body.

Haemorrhage is the most important hazard of all oral anticoagulants including vitamin K antagonists. This risk is increased in patients:

- with 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, hepatic disease and associated coagulopathy, congential or acquired bleeding disorders, severe uncontrolled arterial hypertension.
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins, 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.
- receiving concomitant treatment with other medication associated with a risk of haemorrhage, e.g. antiplatelets or Non Steroidal Anti Inflammatory Drugs (NSAIDs).

In light of the risk of haemorrhage for all anticoagulants, prescribers should consider each individual patient's risk of haemorrhage and closely observe posology recommendations, contraindications, warnings and precautions for use to minimise this risk. This includes a careful benefit-risk assessment in patients with conditions, or undergoing procedures, such as those outlined above, all of which increase the risk of major haemorrhage. In addition, clinical surveillance for signs and symptoms of haemorrhage is recommended throughout the treatment period especially in patients at increased risk.

Renal impairment may constitute a contraindication, or a reason to consider not using these medicines, or reducing the dose. Decreased renal function, age ≥75 years, low body weight and certain concomitant medications are associated with increased plasma levels of the NOACs. Therefore renal function should be assessed and monitored as appropriate, in accordance with the recommendations described in the product information for each of the medicines concerned.

Attention should also be paid to hepatic function. Hepatic 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 medicines.

National Monitoring Experience

The HPRA continues to receive reports of suspected adverse reactions associated with the use of NOACs. The majority of the suspected reactions reported have been consistent with the known potential risks of anticoagulants and the characteristics of the patients treated. Adverse reactions reported include nausea, vomiting, abdominal pain, dizziness and haemorrhagic events that range from bruising, contusions and oozing at wound sites post surgery to gastrointestinal haemorrhage. In many of the more serious cases the patients concerned had significant underlying illness (renal impairment, malignancy, heart failure) or were treated with multiple medicines and/or surgery, which may have contributed to the outcome. In addition many of the cases were influenced by underlying disease or other complications unrelated to the medicine. There have also been some reports of DVT, pulmonary embolism and cardiac effects (e.g. angina, tachycardia etc.), which would not be unexpected in the patient population concerned.

These medicines are subject to additional monitoring and the HPRA, together with EMA, will continue to closely monitor experience with use of NOACs and will highlight any relevant, new information should it become available. Healthcare professionals should report any adverse reactions suspected to be associated with the use of NOACs to the HPRA electronically via the website (www.hpra.ie), using the online or downloadable versions of the Adverse Reaction Report Form. Alternatively reports may be submitted using the post-paid 'Yellow Card' available from the HPRA by telephone (01 676 4971) or fax (01 6762517).

Key Message

- Close clinical surveillance, including monitoring for signs of haemorrhage, to facilitate early intervention and management is recommended for all patients treated with oral anticoagulants.
- Renal and hepatic function should be assessed and monitored during treatment with the NOACs in line with the recommendations in the product information.
- Factors including decreased renal function, age ≥75 years, low body weight and certain concomitant medications are associated with increasing the plasma levels of NOACs. Please refer to the individual product information (SmPC) for further 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.
- 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.

Previous updates highlighting relevant information and recommendations regarding the use of these medicines included as follows:

Drug Safety Newsletter (DSN) Edition 49 August 2012, Edition 56 October 2013 available at www.hpra.ie.

DHPC from Marketing Authorisation Holders for NOACs- September 2013 available at www.hpra.ie.

**Full details of all risk factors are included in the product information for each medicine available at www.hpra.ie and www.ema.europa.eu/ema*