HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Direct-acting oral anticoagulants (DOACs): Update on recent studies and reminder of the importance of adhering to product information, including existing measures to minimise the known risk of haemorrhage

DOACs include the direct factor Xa (activated factor X) inhibitors apixaban (Eliquis), edoxaban (Lixiana and Roteas), and rivaroxaban (Xarelto▼ and generic brands) as well as the direct thrombin inhibitor, dabigatran etexilate (Pradaxa). DOACs* are authorised for the treatment and prevention of thromboembolic events, depending on the individual agent and dose.

The product information for DOACs includes detailed recommendations to minimise the risk of haemorrhage, a known and important risk of all anticoagulants. A retrospective, non-interventional study, using European databases, was carried out at the request of the European Medicines Agency (EMA) to assess the risk of major bleeding associated with the use of DOACs when compared to vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation. Overall, the new data confirm the bleeding patterns of DOACs versus VKA observed in previous clinical trials. The benefit-risk balance remains positive for all three DOACs investigated (apixaban, dabigatran, rivaroxaban) within the authorised indications. There was an observation of increased risk of bleeding in older patients (>75 years), however, the data were not sufficient at this time to recommend additional dosage changes in this population, and further evaluations by the license holders were requested in this regard.

The HPRA previously highlighted information and recommendations in relation to the safe and effective use of DOACs in its Drug Safety Newsletters (Editions 45, 49, 56, 90, 93 and 96).

In relation to national reporting experience, the HPRA continues to receive reports of severe haemorrhage, in some cases fatal, in association with use of DOACs in patients in Ireland. In some cases, underlying risk factors for bleeding events were present. Healthcare professionals are reminded of the importance of consulting full and up-to-date product information when prescribing or administering DOACs.

Drug-drug interactions and risk of haemorrhage

The HPRA has received reports of haemorrhage involving patients who have been co-prescribed DOACs in association with other anticoagulant agents e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, or other DOAC, etc.). Healthcare professionals are reminded that co-administration of DOACs with other anticoagulant agents is **contraindicated** (except under very limited, specific circumstances as detailed in the SmPC for the relevant DOAC). In order to avoid inadvertent exposure to two anticoagulant agents, it is advised that patient medication records are carefully reviewed when prescribing or dispensing DOACs, particularly following transitions of care. Similarly, detailed 'switching' instructions are available in the product information to support a safe transition between anticoagulant therapies.

Concomitant use of DOACs with antiplatelet agents increases the risk of bleeding and caution is also advised if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

Concomitant use of P-glycoprotein inhibitors, and in some cases CYP3A4 inhibitors can increase the circulating levels of DOACs. Therefore, contraindications, dose reduction recommendations or other precautions may be in place depending on the relevant DOAC and interacting drug.

In all cases please refer to the product information for the individual DOAC for detailed information on interacting medicinal products.

Use of DOACs in special populations

DOACs should be used with caution in patients who have an increased risk of haemorrhage. In some cases, reports of haemorrhage received by the HPRA describe patients with existing risk factors. Healthcare professionals are reminded of the importance of adhering to existing prescribing recommendations in special populations. **Elderly** patients, patients with **renal impairment** (see below), and those with **low body weight (under**

60 kg), are at particular risk of haemorrhage. Contraindications and cautions may apply in case of certain **hepatic conditions**.

Patients with gastritis, esophagitis or gastroesophageal reflux may be at increased risk of gastrointestinal bleeding, however, recommendations differ between DOACs.

Prescribers are advised to consider each individual patient's risk of haemorrhage and closely observe posology recommendations, contraindications, and warnings and precautions for use, which are described in detail in the product information for each of these medicines, accessible from the HPRA website. Patients (particularly those with an increased bleeding risk) should be advised of the risk of bleeding and be routinely examined clinically for signs of bleeding or anaemia. Bleeding can occur at any site during treatment with DOACs and treatment should be discontinued if severe haemorrhage occurs. The product information for the individual DOACs includes further guidance in this regard.

DOACs are not recommended for patients with antiphospholipid syndrome due to a possible increased risk of recurrent thrombotic events. Contraindications or warnings with regard to the use of DOACs in patients with prosthetic heart valves are also included in the product information for each of the authorised DOACs.

Impaired renal function

DOAC exposure is increased in patients with renal impairment. It is important that patients receive an appropriate dose depending on renal function. Prescribers should be aware that dose adjustment may be necessary if renal function significantly changes during treatment e.g. due to increasing age, hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products. For adult patients prescribed DOACs, renal function should be calculated using the creatinine clearance (CrCl). For paediatric populations, it is important that the individual product information for the relevant DOAC is consulted for specific recommendations on measurement of renal function and dose determination.

The prescriber guide for Lixiana (edoxaban) has recently been updated to highlight the importance, as for all DOACs, of measuring creatinine clearance, as well as body weight, and the need for both parameters to be regularly checked during treatment. More information on how to access educational materials for DOACs may be found below.

The product information for each individual DOAC should be consulted for detailed information on dose adjustment, cautions, and contraindications in renal impairment.

Educational Materials for DOACs

Educational materials to further support safe prescription, dispensing and use of DOACs, and previously circulated to healthcare professionals by the relevant marketing authorisation holders (MAH), are available on www.hpra.ie. Tools such as prescriber guides and patient alert cards are available in electronic format from the HPRA website, by searching for the named DOAC in the 'Find a Medicine' searchbox, and clicking on 'EdM' in the search results. Additional hard copy versions of educational materials may be obtained by contacting the relevant MAH. It is important that healthcare professionals prescribing and dispensing DOACs are aware of the available educational materials and ensure that patients are supplied with a copy of the up-to-date materials for patients. Educational materials for DOACs are intended to provide clear information on the nature of specific risks (e.g. haemorrhage) and actions required to prevent and/or minimise such risks and are updated on an ongoing basis. These materials complement, rather than replace, the full product information.

Key Message

Haemorrhage is a known important risk associated with all oral anticoagulants. Prescribers should consider each individual patient's risk of haemorrhage and closely observe posology recommendations, contraindications, warnings and precautions for use, which are described in detail in the product information for each of these medicines, accessible from www.hpra.ie.

Consider **patient specific factors (which may evolve over time)** when prescribing DOACs. Caution is advised when prescribing DOACs to patients at increased risk of bleeding (e.g. elderly patients, patients with renal impairment, patients with a low body weight (under 60kg), and patients with gastritis, esophagitis, or gastroesophageal reflux).

For adult patients prescribed DOACs, renal function should be calculated using the creatinine clearance (CrCl). For paediatric populations, it is important that the individual product information for the relevant DOAC is consulted for specific recommendations on measurement of renal function and dose determination.

Educational materials are available to support safe prescription, dispensing and use of DOACs.

Suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

**Further information on DOACs indications is available from the www.hpra.ie and www.ema.europa.eu.*