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HPRA DRUG SAFETY NEWSLETTER

105TH EDITION

In this Edition

Pregabalin – Respiratory depression without concomitant use of opioids or other CNS depressants

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded, as part of a routine review of safety data, that pregabalin has been associated with reports of respiratory depression in the absence of concomitant therapy with opioids or other central nervous system (CNS) depressants, in patients with and without other risk factors for respiratory depression.

Pregabalin-containing medicinal products* are licensed in Ireland under various brand names for the treatment of neuropathic pain in adults, as adjunctive therapy in adults for specific forms of epilepsy and for generalised anxiety disorder in adults.

Concomitant use of pregabalin with opioids and/or other CNS depressants has been associated with reports of respiratory failure, coma and deaths. The product information for pregabalin-containing medicinal products reflected this risk and advised caution when prescribing pregabalin concomitantly with opioids due to the risk of CNS depression, noting that a case-control study of opioid users found that concomitant use of pregabalin with an opioid was associated with an increased risk for opioid-related death compared to opioid use alone. The recent PRAC review of safety data considered reports of respiratory depression without concomitant use of opioids or CNS depressants, in patients with and without other risk factors for respiratory depression. Having considered the available evidence, PRAC concluded that pregabalin has also been associated with severe respiratory depression in the absence of concomitant opioid and/or other CNS depressant use in patients with and without risk factors for respiratory depression.

Patients with the following risk factors may be at higher risk of experiencing respiratory depression with pregabalin and dose adjustment may be necessary:

- Compromised respiratory function;
- Respiratory or neurological disease;
- Renal impairment;
- Concomitant use of CNS depressants;
- Older age (> 65 years)

Patients are advised to contact their doctor if they experience trouble breathing or shallow breaths. It is advised not to drink alcohol while taking pregabalin.

The product information (summary of product characteristics (SmPC) and package leaflet (PL)) for pregabalin-containing medicinal products will be updated to include new warnings on respiratory depression and to add it as a possible adverse reaction with a frequency of 'not known'.

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Advice to Healthcare Professionals

- There have been reports of severe respiratory depression in association with pregabalin, including cases without use of concomitant opioids or other CNS depressants, and in the absence of other risk factors. The frequency of this adverse reaction is not known.
- Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of respiratory depression and dose adjustments may be necessary in these patients.

Key Message

There have been reports of severe respiratory depression in relation to pregabalin use, including cases without concomitant opioid use or other risk factors.

Dose adjustments may be necessary in patients at higher risk of respiratory depression (e.g. patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants, and in those of older age).

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for pregabalin-containing medicinal products will be updated to reflect this information and to include respiratory depression as an adverse reaction with a frequency of 'not known'.

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

** Further details on pregabalin-containing medicines including Lyrica and generics are available at www.hpra.ie and www.ema.europa.eu.*

Direct oral anticoagulants (DOACs) – Reminder of the importance of adhering to product information and existing measures to minimise the known risk of haemorrhage

Direct oral anticoagulants (DOACs) include the direct factor Xa (activated factor X) inhibitors apixaban (Eliquis and generic brands), 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 HPRA previously highlighted information and recommendations in relation to the safe and effective use of DOACs in Drug Safety Newsletters (Editions 45, 49, 56, 64, 90, 93 and 96). These articles focused on contraindications for concomitant administration of DOACs with other anticoagulants, use in special populations, including the elderly (>75 years), and in those with impaired renal function. Editions 90 and 96 specifically highlighted that rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves**, including patients who have recently undergone transcatheter aortic valve replacement (TAVR).

New data from a retrospective, non-interventional study using European databases, 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, confirmed the bleeding patterns of DOACs versus VKAs previously observed in 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 for dabigatran and rixaroxaban 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.

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. The product information for DOACs includes detailed recommendations to minimise the risk of haemorrhage, a known and important risk of all anticoagulants. Healthcare professionals are reminded of the importance of consulting full and up-to-date product information when prescribing or administering DOACs. Key recommendations to reduce the risk of haemorrhage are described below.

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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 summary of product characteristics (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. 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 noradrenaline reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

Concomitant use of P-glycoprotein (P-gp) 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 (< 60 kg)**, are at particular risk of haemorrhage. Contraindications and cautions may apply in case of certain **hepatic conditions**.

Patients with gastritis, oesophagitis 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 DOAC includes further guidance in this regard.

As described in HPRA Drug Safety Newsletter Edition 93, DOACs are not recommended for patients with antiphospholipid syndrome (APS) due to a possible increased risk of recurrent thrombotic events.

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 dose determination of **DOACs in adults**, renal function should **be determined using the calculated 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.

Monitoring of exposure

Although treatment with DOACs does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of the exposure to a Factor Xa inhibitor DOAC (apixaban, edoxaban, or rivaroxaban) may help to inform clinical decisions, e.g. overdose and emergency surgery. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information on dabigatran related anticoagulation, but results should be interpreted with caution due to inter-test variability.

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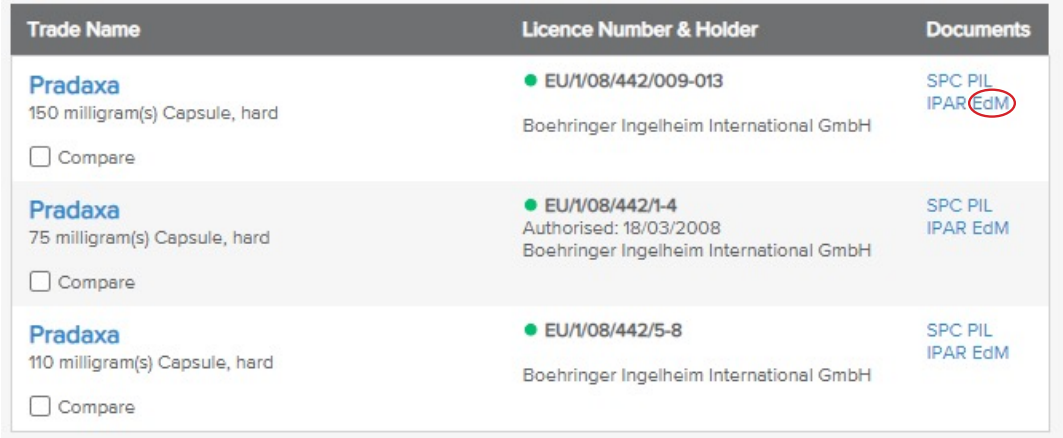
The international normalised ratio (INR) test is unreliable in patients on dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Specific reversal agents are approved for dabigatran (Praxbind (idarucizumab)) and apixaban and rivaroxaban (Ondexxya▼ (andexanet alfa)), however no specific reversal agent is currently authorised for edoxaban. Following administration of Ondexxya▼ (andexanet alfa), it should be noted that commercial anti-Factor Xa assays are unsuitable for measuring anti-Factor Xa activity and result in a substantial underestimation of the reversal activity of andexanet alfa. Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response, lack of efficacy and adverse events.

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 (see Fig. 1). 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.

Figure 1 – Accessing educational materials (EdM) on the HPRA website, www.hpra.ie



Key Message

Haemorrhage is a known important risk associated with all oral anticoagulants. Healthcare professionals should consider each individual patient's risk of haemorrhage when prescribing and dispensing DOACs, 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 (<60kg), and patients with gastritis, oesophagitis, or gastroesophageal reflux).

For dose determination of **DOACs in adults**, renal function should **be determined using the calculated 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.

Quantitative anti-Factor Xa assays may be useful in exceptional situations where knowledge of the exposure to a Factor Xa inhibitor DOAC may help to inform clinical decisions. Specific tests may be used to provide useful information on dabigatran related anticoagulation. Specific **reversal agents** are approved for dabigatran, apixaban and rivaroxaban.

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 DOAC indications is available from the www.hpra.ie and www.ema.europa.eu.*

** *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.*

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Reporting of suspected adverse reactions

Healthcare professionals, patients and carers are asked to continue to report suspected adverse reactions to the HPRA via the available options at www.hpra.ie/report. Reporting suspected adverse reactions, even those known to occur in association with a medicinal product, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

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

PRODUCT	SAFETY ISSUE
Belkyra (deoxycholic acid)	Risk of injection site necrosis

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority