9th September 2013

Dear Health Care Provider,

The new oral anticoagulants Eliquis®, Pradaxa®, Xarelto®
Beware of the risk factors for bleeding, pay attention to posology, contraindications, and warnings and precautions for use to reduce the risk of bleeding

Eliquis® (apixaban), Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban) are oral anticoagulants which in recent years have been authorised for indications where vitamin K antagonists (warfarin, phenprocoumon and acenocoumarol) or low molecular weight heparins (LMWH) have been used for decades. Unlike vitamin K antagonists, there is no need for routine monitoring of anticoagulant activity when administering these new medicines.

However, 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 the new oral anticoagulants. Furthermore, post-marketing reports indicate that not all prescribers are sufficiently aware of the product information in terms of managing bleeding risks.

The information provided in this letter has been reviewed and endorsed by the European Medicines Agency (EMA) and the Irish Medicines Board (IMB).

Recommendations

In light of the above, prescribers should consider the individual patient risk of bleeding and observe posology, contraindications, and warnings and precautions for use. While differences in contraindications exist between the new oral anticoagulants, they share the following contraindications:

- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include 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 (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, other) except under the circumstances of switching therapy to or from the medicine, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter

Please refer to the respective product information for Eliquis®, Pradaxa® and Xarelto® for information about additional contraindications specific to each medicine. Copies of the Summary of Product Characteristics can be obtained by electronic download from www.medicines.ie.

It is important to pay attention to the recommended posology and the 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 (such as NSAIDs and antiplatelets), which increase the risk of

major bleeding. In addition, clinical surveillance for signs and symptoms of bleedings is recommended throughout the treatment period, particularly in patients at increased risk of bleeding.

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 their dose. Please refer to the product information since recommendations differ between the three medicines.

There is currently no specific antidote available for Eliquis®, Pradaxa® or Xarelto®. The product information for each product includes advice on treatment in the event of bleeding complications.

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Eliquis®, Pradaxa® or Xarelto® 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 or they may be reported by telephone (01 676 4971) or fax (01 676 2517).

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates. Any suspected adverse reactions may also be reported to Bristol-Myers Squibb for Eliquis® (telephone: 1 800 749 749, e-mail: medical.information@bms.com); Boehringer Ingelheim for Pradaxa® (telephone: 01 291 3960, fax: +44 1344 742661, e-mail: PV_local_UK_Ireland@boehringer-ingelheim.com); or Bayer Ltd for Xarelto® (telephone: 01 2999 313, fax: 01 2061 456, e-mail: adr-ireland@bayerhealthcare.com).

Should you require any further information, please contact Bristol-Myers Squibb Medical Information for Eliquis® (telephone: 1 800 749 749, e-mail: medical.information@bms.com); Boehringer Ingelheim Medical Information for Pradaxa® (telephone: 1850 946100, e-mail: medinfo.bra@boehringer-ingelheim.com); or Bayer Ltd Medical Information for Xarelto® (telephone: 01 2999 313, fax: 01 2061 456, e-mail: info.ireland@bayerhealthcare.com).

Sincerely yours,

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Dr Declan O'Callaghan
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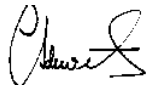

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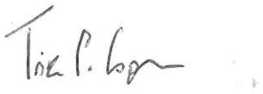

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