20th May 2019

Direct Healthcare Professional Communication

Apixaban (Eliquis), dabigatran etexilate (Pradaxa), edoxaban (▼ Lixiana) and rivaroxaban (▼ Xarelto) are not recommended in patients with antiphospholipid syndrome due to possible increased risk for recurrent thrombotic events

Dear Healthcare Professional,

Bayer AG, Daiichi Sankyo Europe GmbH, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb/Pfizer EEIG in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- **In patients with a history of thrombosis diagnosed with antiphospholipid syndrome (APS) use of rivaroxaban has been associated with an increased risk of recurrent thrombotic events, compared with warfarin. Other DOACs (apixaban, edoxaban and dabigatran etexilate) may be associated with a similarly increased risk of recurrent thrombotic events, compared to a vitamin K antagonist such as warfarin.**
- **DOACs are not recommended in patients with APS, particularly high-risk patients (those who test positive for all three antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies).**
- **Review whether continued treatment is appropriate for patients with APS currently receiving a DOAC for preventing thromboembolic events, in particular high-risk patients, and consider switching to a vitamin K antagonist.**

Background on the safety concern

The level of evidence for increased risk of recurrent thrombotic events in patients diagnosed with APS differs among the marketed direct oral anticoagulants (DOACs). Currently, there is not enough evidence that any DOAC offers sufficient protection in patients with established APS, particularly in those at highest risk for thromboembolic events. The use of DOACs in these patients is not recommended.

Rivaroxaban: In an investigator sponsored randomised open-label multicentre study (TRAPS, (registered at www.clinicaltrials.gov as #NCT02157272; Blood. 2018 Sep 27;132 (13):1365-1371) with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with APS and at high risk for thromboembolic events (persistently tested

positive for all 3 antiphospholipid tests). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of thromboembolic events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance <50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic stroke and 3 myocardial infarctions). No thromboembolic events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

Apixaban, edoxaban and dabigatran etexilate: The available data for these products are more limited, as there are no completed clinical trials of these products in patients with APS. There is an ongoing investigator sponsored research study specifically designed for studying patients with APS on apixaban (ASTRO-APS - Apixaban for the Secondary Prevention of Thrombosis among Patients with Antiphospholipid Syndrome) from which the final results are not yet available.

Further information

Approved indications in adults for all DOACs include treatment and prevention of venous thromboembolism (VTE) and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with additional risk factor(s). Apixaban, dabigatran etexilate and rivaroxaban are also approved for prevention of VTE in conjunction with hip or knee replacement surgery. Rivaroxaban is also approved, in addition to acetylsalicylic acid (aspirin), in patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events, and in addition to acetylsalicylic acid or acetylsalicylic acid plus clopidogrel or ticlopidine, after an acute coronary syndrome event.

The Product Information for these products will be amended to include a new warning regarding APS patients.

Call for reporting

Rivaroxaban and edoxaban are subject to additional monitoring ▼. This will allow quick identification of new safety information.

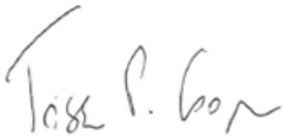
Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E- mail: medsafety@hpra.ie . Reports of suspected adverse reactions can also be made to the companies, contact details below.

Company contact point

If you have any questions, or if you require any further information, please contact the medical information service of the relevant Marketing Authorisation Holder:

Marketing Authorisation Holder	Product Name	Email address	Phone number
Bristol-Myers Squibb Pharma/Pfizer EEIG	Eliquis (Apixaban)	medical.information@bms.com	+353 1 800 749 749
Daiichi Sankyo Europe GmbH	Lixiana (Edoxaban)	MEDINFO@daiichi-sankyo.ie	+353 1 489 3000
Boehringer Ingelheim International GmbH	Pradaxa (Dabigatran etexilate)	medinfo.bra@boehringer-ingelheim.com	+353 1 295 9620
Bayer AG	Xarelto (Rivaroxaban)	Info.ireland@bayerhealthcare.com	+353 1 216 3300

Yours faithfully,



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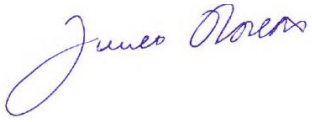

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