**Direct Healthcare Professional Communication**

**Subject: Direct Healthcare Professional Communication (DHPC) for the Direct Oral Anticoagulants (DOACs) Apixaban, Edoxaban, Dabigatran and Rivaroxaban for dissemination in Saudi Arabia.**

Date: 12 Jun 2019

Dear Healthcare Professional,

Bayer Saudi Arabia LLC, SAJA Pharmaceuticals Co. Ltd., Boehringer Ingelheim Middle East & Africa GmbH, Bristol-Myers Squibb/Pfizer EEIG in agreement with the Saudi Food and Drug 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.

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.

**Reporting adverse drug reactions**

Reporting of adverse drug reactions will allow for quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to:

**National Pharmacovigilance and Drug Safety Centre**
**SFDA call center:** 19999
**Toll free:** 8002490000
**Fax:** +9661 1 2057662
**E-Mail:** npc.drug@sfda.gov.sa
**Online:** http://ade.sfda.gov.sa/

Or

**Pharmacovigilance department in Bayer Saudi LLC:**
Bayer Saudi Arabia LLC.
Al Kamal Import Office
Ittihad St. P.O Box 15369
21444 Jeddah, Saudi Arabia
**Tel.:** +966 126573015
**Fax:** +9661 2 6534992
**Email:** pv.me@bayer.com
**For medical inquiries:** med-info.me@bayer.com

**Pharmacovigilance department at Pfizer Saudi Limited:**
Email: SAU.AEReporting@Pfizer.com
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MedInfoMEandAfrica@pfizer.com
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Sincerely,

A. Rahman 30 Jun 2019

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Roa 25 June 19

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25/June/2019

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