IMPORTANT MEDICINE SAFETY INFORMATION

Dear Healthcare Professional,

Important safety information on the treatment of patients with antiphospholipid syndrome (APS) and the use of rivaroxaban (Xarelto®) Possible increased risk for recurrent thrombotic events

Bayer (Pty) Ltd, in agreement with the South African Health Products Regulatory Authority (SAHPRA) would like to inform you of the following:

In patients with a history of thrombosis diagnosed with antiphospholipid syndrome (APS); use of Xarelto® (rivaroxaban) has been associated with an increased risk of recurrent thrombotic events, compared with warfarin.

Xarelto® (Rivaroxaban) is not recommended in patients with antiphospholipid syndrome, especially high-risk patients (those who test positive for all three antiphospholipid tests - lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein I antibodies), where the use of Xarelto® is contraindicated.
Please review whether continued treatment is appropriate for patients with APS currently receiving Xarelto®, for preventing thromboembolic events'; in particular, high-risk patients mentioned above. Where appropriate, please consider switching to a vitamin K antagonist. Currently, there is not enough evidence that any direct oral anticoagulant (DOAC / NOAC) offers sufficient protection in patients with established APS, particularly in those at highest risk for thromboembolic events.

Background on the safety concern
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 target 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.

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Regulatory Affairs Department

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The Professional Information and the Patient Information Leaflet for Xarelto® will be amended to include new safety information regarding APS patients as reflected in the paragraph below.

'Treatment with rivaroxaban in patients with persistent triple positive antiphospholipid syndrome (APS)' is contraindicated.
Treatment of patients with established APS is not recommended as evidence regarding safety and efficacy, including the benefit/harm balance of rivaroxaban (and DOACs with the same mechanism of action) in APS patients, is inconclusive. There is some evidence that treatment of persistently triple positive APS patients with rivaroxaban is associated with an increased risk of recurrent arterial thrombotic events compared with treatment of these patients with warfarin; a vitamin K antagonist (see Contraindications).

Products to be updated	Active Ingredient(s)	Reg. Number
Xarelto® 10	Rivaroxaban 10 mg	42/8.2/1046
Xarelto® 15	Rivaroxaban 15 mg	46/8.2/0111
Xarelto® 20	Rivaroxaban 20 mg	46/8.2/0112

Reporting adverse drug reactions and safety information

Healthcare professionals should report all adverse events suspected to be associated with the use of **Xarelto®** to:

South African Health Products Regulatory Authority **(SAHPRA)**
Pretoria
Tel: (012) 842 7609/10 e-mail: adr@sahpra.org.za
or
the National Adverse Drug Event Monitoring Centre (NADEMC)
Tel: (021) 447 1618 or Fax (021) 448 6181

Bayer (Pty) Ltd:

Pharmacovigilance Unit
Telephone: 011 921 5167
Facsimile: 086 681 2289
Mobile: 082 894 3048
Email: zapv@bayer.com

or

Medical Queries/Information
Telephone: 011 921 5514
Facsimile: 086 677 8393
Mobile: 082 894 3048
Email: za-medinfo@bayer.com

Yours faithfully,
Bayer (Pty) Ltd

Eric Chauke
Regulatory Affairs Head/CQH
Responsible Pharmacist

Dr. Naren Jairam
Medical Director