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Direct Healthcare Professional Communication

Rivaroxaban (Rivaroxaban Sandoz) is not recommended in patients with antiphospholipid syndrome due to possible increased risk for recurrent thrombotic events

Dear Healthcare Professional,

Sandoz Pharmaceuticals d.d., in agreement with the European Medicines Agency and Malta Medicines 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

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with direct anticoagulants in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt, or alternatively an adverse event can be reported to

Company	Email	Phone
Sandoz	drug_safety.malta@novartis.com	+356 21222872

▼Rivaroxaban is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reaction.

Company contact point

Should you have any question or require additional information, please call Medical Information at:

Company	Product Name	Email	Phone
Sandoz	Rivaroxaban Sandoz 10mg film coated Tablets Rivaroxaban Sandoz 15mg film coated Tablets Rivaroxaban Sandoz 20mg film coated Tablets	regvjsp@vjsalomone.com	+356 99644126

Yours faithfully,

Post-Licensing Directorate

Medicines Authority