3 October 2018

Rivaroxaban (Xarelto▼): Increase in all-cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement in a prematurely stopped clinical trial.

Dear Healthcare Professional,

Bayer AG, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of the preliminary results of the GALILEO trial:

Summary

- **A phase III clinical study, 17938 (GALILEO), in patients after transcatheter aortic valve replacement (TAVR) has been terminated early based on preliminary results showing an increase in all-cause mortality, thromboembolic and bleeding events in rivaroxaban-treated patients. Analyses are ongoing.**
- **Rivaroxaban is not approved for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients.**
- **Rivaroxaban treatment should be stopped in patients who undergo TAVR, and switched to standard of care.**

Background on the safety concern

The study 17938 (GALILEO) is a randomised, open label, active-controlled, multicentre phase III trial to evaluate clinical outcomes after successful transcatheter aortic valve replacement (TAVR) in subjects randomised to either a rivaroxaban-based anticoagulation strategy or an antiplatelet-based strategy. The first group received rivaroxaban 10 mg once daily and acetylsalicylic acid (ASA) 75-100 mg once daily for 90 days followed by maintenance with rivaroxaban 10 mg once daily, whereas the comparator group was given clopidogrel 75 mg and ASA 75-100 mg once daily for 90 days followed by ASA alone.

The primary efficacy endpoint is a composite of all-cause death, stroke, systemic embolism, myocardial infarction, pulmonary embolism, deep vein thrombosis and symptomatic valve thrombosis and the primary safety endpoint is a composite of life-threatening or disabling (BARC

types 5 and 3b/3c) and major (BARC type 3a) bleeding events. Patients with atrial fibrillation at randomisation were excluded from this trial.

In August 2018, the independent Data Safety Monitoring Board (DSMB) recommended stopping the trial, as a preliminary analysis of available data suggested an imbalance between the two study groups in all-cause mortality, thromboembolic and bleeding events. **The incidences in the rivaroxaban group (826 patients) and the antiplatelet group (818 patients), respectively, were 11.4% versus 8.8% for death or first thromboembolic events, 6.8% versus 3.3% for all-cause death and 4.2% versus 2.4% for primary bleeding events.** These results are preliminary and based on incomplete data collection. The final study data will be assessed by regulatory authorities as soon as they are available, including an assessment of any implications for approved indications.

TAVR is performed in patients in need of an aortic valve replacement but at higher risk for standard open heart valve surgery. Patients undergoing TAVR also present with clinical risk factors pertinent to the background disease of aortic valve stenosis.

Xarelto is not approved for thromboprophylaxis in patients with prosthetic heart valves, including patients having undergone TAVR, and should not be used in such patients.

The approved indications for Xarelto are as follows:

Rivaroxaban (Xarelto) 2.5 mg, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers; and co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Xarelto 10 mg is authorised for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Xarelto 15 mg and Xarelto 20 mg are authorised for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Xarelto 10 mg, Xarelto 15 mg and Xarelto 20 mg are authorised for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the MHRA through the Yellow Card Scheme, website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary); by emailing yellowcard@mhra.gov.uk; at the back of the British National Formulary (BNF); by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789; or by downloading and printing a form from the Yellow Card website.

Adverse events should also be reported to Bayer plc. Tel.: 0118 206 3500, Fax.: 0118 206 3703, Email: pvuk@bayer.com

Company contact point

If you have any questions, or if you require any further information, please contact the medical information service of Bayer plc:

- Telephone: 0118 206 3116
- E-mail: medical.information@bayer.co.uk

Yours faithfully,

Dr Luis Felipe Graterol

Medical Director

Bayer plc