Important Safety Information XARELTO (rivaroxaban)
Increase in all cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement

2018-12-20

Audience
Interventional cardiologists and hospital cardiologists, at all hospitals that perform interventional cardiology procedures.

Key messages

- **Increased all-cause mortality, thromboembolic and bleeding events have been reported in a phase III clinical study among XARELTO-treated patients who had transcatheter aortic valve replacement (TAVR).**
- **Based on these preliminary results, the clinical study has been terminated and further analysis of the study results is ongoing.**
- **Healthcare professionals are reminded that:**
    - **XARELTO is not authorized for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients.**
    - **XARELTO treatment should be stopped in patients who undergo TAVR and switched to standard of care.**

What is the issue?
In August 2018, the Data Safety Monitoring Board (DSMB), while monitoring patient safety independently in the phase III clinical study (GALILEO) in patients after transcatheter aortic valve replacement (TAVR), recommended stopping the study based on preliminary results showing an increase in all-cause mortality, thromboembolic and bleeding events in XARELTO-treated patients.

Products affected
XARELTO (rivaroxaban) 2.5 mg, 10 mg, 15 mg and 20 mg tablets

Background information

XARELTO (rivaroxaban 10 mg, 15 mg, and 20 mg tablets) is indicated in Canada for the:

- prevention of venous thromboembolic events in patients who have undergone elective total hip replacement (THR) or total knee replacement surgery;
- treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE; and
- prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

XARELTO (rivaroxaban 2.5 mg tablet), in combination with 75 mg – 100 mg acetylsalicylic acid (ASA), is also indicated in Canada for:

- prevention of stroke, myocardial infarction and cardiovascular death, and for prevention of acute limb ischemia and mortality in patients with coronary artery disease with or without peripheral artery disease.

GALILEO is a randomized, open label, active-controlled, multicentre phase III trial to evaluate clinical outcomes after successful TAVR in subjects randomized to either a XARELTO-based anticoagulation strategy or an antiplatelet-based strategy. The first group received XARELTO 10 mg once daily and ASA 75-100 mg once daily for 90 days, followed by maintenance with XARELTO 10 mg once daily. 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, PE, DVT, and symptomatic valve thrombosis. The primary safety endpoint is a composite of life-threatening or disabling and major bleeding events. Patients with atrial fibrillation were excluded from this trial.

In August 2018, the independent Data Safety Monitoring Board recommended stopping the trial, as a preliminary analysis of available data suggested a numerical imbalance between the two study groups in all-cause mortality, thromboembolic and bleeding events. The incidences in the XARELTO 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 as soon as they are available, including an assessment of any implications for approved indications.

TAVR is performed in patients who need an aortic valve replacement but who are at too high a risk for a standard open heart valve surgery. Patients undergoing TAVR present with multiple 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.

Information for consumers
XARELTO is not recommended in patients who have an artificial heart valve or had artificial aortic valve replacement.

Patients and caregivers should discuss any questions or concerns about this information with their healthcare professional.

Patients receiving XARELTO should also inform their healthcare professional if they experience any side effects.

Information for health care professionals
Healthcare professionals are reminded that:

- XARELTO 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.
- XARELTO treatment should be stopped in patients who undergo TAVR, and they should be switched to standard of care.

Action taken by Health Canada
Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (www.healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php). This communication update will be further distributed through the MedEffect™ e-Notice email notification system.

Report health or safety concerns
Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of death, thromboembolic and bleeding events or other serious or unexpected side effects in patients receiving XARELTO should be reported to BAYER Inc. or Health Canada.

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, ON
L4W 5R6
Telephone: 1-800-265-7382
Online: Reporting Side Effects (http://www.bayer.ca/en/about-bayer/contact-us/#PH)

To correct your mailing address or fax number, contact Bayer Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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