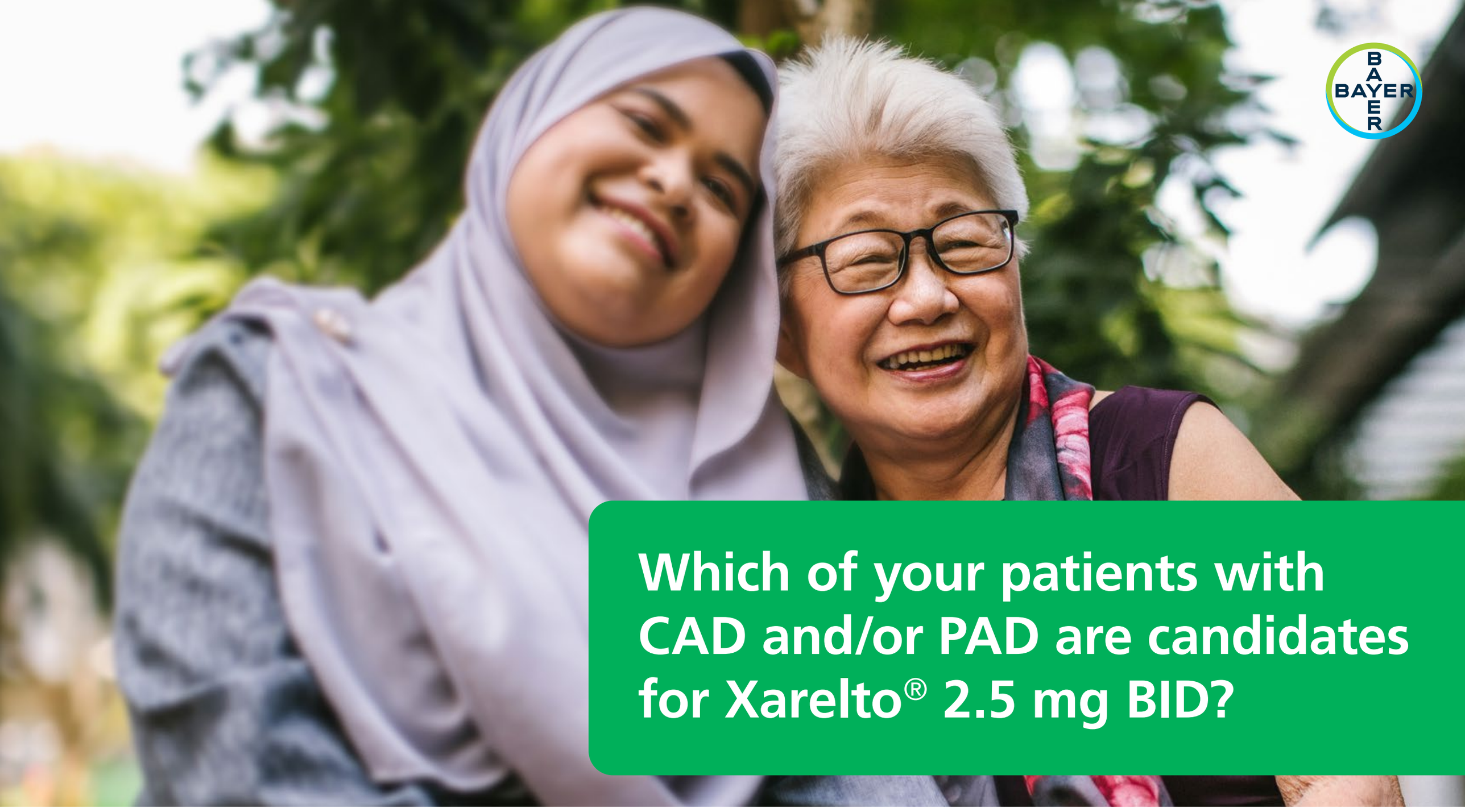


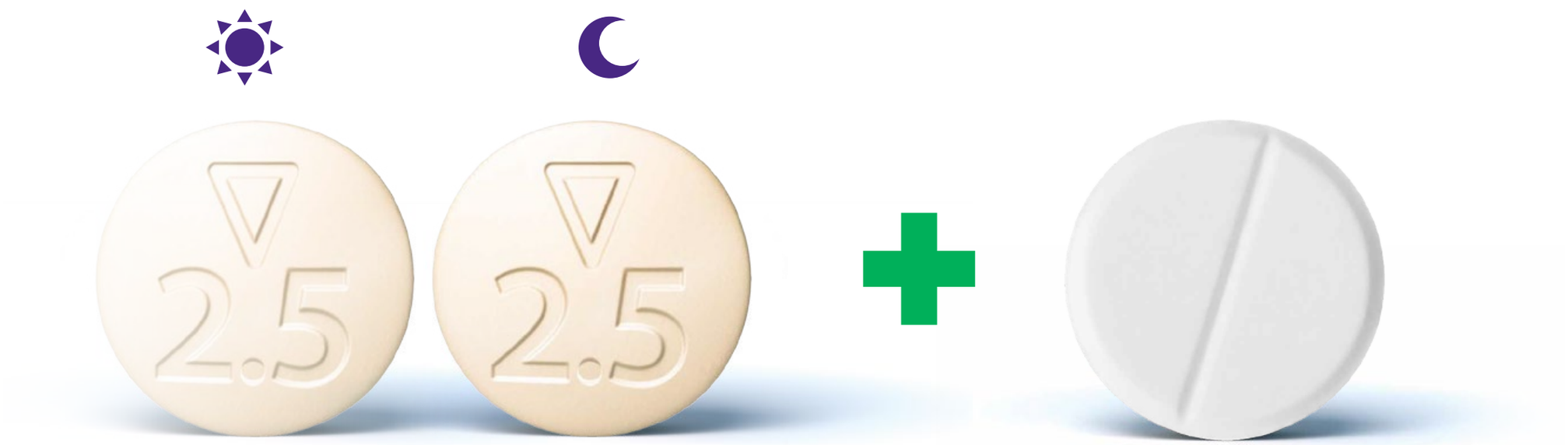
Which of your patients with CAD and/or PAD are candidates for Xarelto® 2.5 mg BID?

[Pr]Xarelto® (rivaroxaban) film-coated tablet (2.5 mg), in combination with 75 mg–100 mg acetylsalicylic acid (ASA), is indicated for the:

- prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD).
- prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

Xarelto® rivaroxaban tablet

Xarelto® 2.5 mg BID in combination with 75-100 mg ASA OD†



Xarelto®
2.5 mg BID

ASA
75-100 mg OD

Xarelto® 2.5 mg BID is not indicated in combination with DAPT.

OD: once daily; BID: twice daily; DAPT: dual antiplatelet therapy
† Please consult the Product Monograph for complete dosing and administration information.

Is your patient eligible to receive the vascular protection regimen of Xarelto® 2.5 mg BID in combination with ASA?

- For the prevention of stroke, MI, CV death, acute limb ischemia and mortality in patients with CAD with or without PAD
- For the prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE

In the COMPASS trial†, CAD was defined as:[2]

- ☐ Myocardial infarction within the last 20 years, or
- ☐ Multi-vessel coronary disease* with symptoms or with history of stable or unstable angina, or
- ☐ Multi-vessel percutaneous coronary intervention (PCI), or
- ☐ Multi-vessel coronary artery bypass graft (CABG) surgery

* Refers to stenosis of greater than or equal to 50% in 2 or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g. exercise or pharmacologic) suggestive of significant ischemia in 2 or more coronary territories; or in 1 coronary territory if at least one other territory has been revascularized.

In the COMPASS trial†, PAD was defined as:[2]

- ☐ Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infra-inguinal arteries, or
- ☐ Previous limb or foot amputation for arterial vascular disease, or
- ☐ History of intermittent claudication and one or more of the following:
  1) An ankle/arm blood pressure (BP) ratio <0.90, or
  2) Significant peripheral artery stenosis (≥50%) documented by angiography, or by duplex ultrasound, or
- ☐ Previous carotid revascularization or asymptomatic carotid artery stenosis ≥50% as diagnosed by duplex ultrasound or angiography.

Xarelto® is indicated in patients with CAD with or without PAD, and in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE.

Inclusion criteria in the COMPASS trial[1†‡]

- ☐ Established CAD
- ☐ Established PAD[‡§]
- ☐ A combination of CAD and PAD

If younger than 65 years old:

- ☐ documentation of atherosclerosis involving at least two vascular beds

OR

- ☐ have at least two additional cardiovascular risk factors:
  - current smoker
  - diabetes mellitus
  - eGFR <60 mL/min
  - heart failure
  - non-lacunar ischemic stroke ≥1 month earlier

Select exclusion criteria in the COMPASS trial[1†‡]

- ☐ high risk of bleeding
- ☐ need of dual antiplatelet therapy
- ☐ need for other non-ASA antiplatelet therapies
- ☐ need for other oral anticoagulant therapies
- ☐ stroke within 1 month
- ☐ history of hemorrhagic or lacunar stroke
- ☐ eGFR <15 mL/min

BID: twice daily; ASA: acetylsalicylic acid; MI: myocardial infarction; CV: cardiovascular; CAD: coronary artery disease; PAD: peripheral artery disease; MALE: major adverse limb events; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; BP: blood pressure; eGFR: estimated glomerular filtration rate

† A pivotal phase III double-blind study investigating the efficacy and safety of Xarelto® 2.5 mg BID + ASA (100 mg OD) (n=9,152) and ASA alone (n=9,126) for the prevention of the composite of stroke, myocardial infarction, or cardiovascular death in patients with stable atherosclerotic vascular disease. Patients with established CAD, PAD or a combination of CAD and PAD were eligible. Coronary artery disease patients <65 years old were required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoker, diabetes mellitus, an eGFR <60 mL/min, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients in need of dual antiplatelet, other non-ASA antiplatelet, or oral anticoagulant therapies as well as patients with a history of ischemic, non-lacunar stroke within 1 month, any history of hemorrhagic or lacunar stroke, or patients with eGFR <15 mL/min were excluded from the study. Mean duration of follow-up was 23 months.[1]

‡ The inclusion and exclusion criteria are based on the criteria used in the COMPASS trial and not based on the indication in Canada. The lists might not be exhaustive.

§ Xarelto® is indicated in patients with CAD with or without PAD, and in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE.

Xarelto® rivaroxaban tablet

Indications and clinical use:

Xarelto® (rivaroxaban) film-coated tablet (10 mg, 15 mg, 20 mg) is indicated for the:

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

Xarelto® (rivaroxaban) film-coated tablet (2.5 mg), in combination with 75 mg-100 mg acetylsalicylic acid (ASA), is indicated for the:

- prevention of stroke, myocardial infarction (MI) and cardiovascular (CV) death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD).
- prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

Xarelto® (rivaroxaban) granules for oral suspension (1 mg/mL) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.

Xarelto® (rivaroxaban) film-coated tablet (15 mg) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulant treatment.

Xarelto® (rivaroxaban) film-coated tablet (20 mg) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulant treatment.

For the treatment of VTE, Xarelto® is **not** recommended as an alternative to unfractionated heparin in patients with pulmonary embolus who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of Xarelto® have not been established in these clinical situations.

In children less than 18 years of age, the safety profile and efficacy of Xarelto® have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, Xarelto® is not recommended for use in children below 18 years of age for indications other than the treatment of VTE and prevention of VTE recurrence.

The safety and efficacy of Xarelto® 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age, therefore, Xarelto® 2.5 mg and 10 mg fill-coated tablets are not recommended in this patient population.

Contraindications:

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis
- Concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-glycoprotein (P-gp), such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir
- Concomitant treatment with any other anticoagulant, including:
  - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
  - low-molecular-weight heparins (LMWH), such as enoxaparin and dalteparin,
  - heparin derivatives, such as fondaparinux, and
  - oral anticoagulants, such as warfarin, dabigatran, apixaban, edoxaban, except under circumstances of switching therapy to or from Xarelto®.
- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk
- Pregnancy
- Nursing women
- Hypersensitivity to Xarelto® (rivaroxaban) or to any ingredient in the formulation

Most serious warnings and precautions:

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING XARELTO®, INCREASES THE RISK OF THROMBOTIC EVENTS. To reduce this risk, consider coverage with another anticoagulant if Xarelto® is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Bleeding: Xarelto®, like other anticoagulants, should be used with caution in patients with an increased bleeding risk. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed Xarelto®. **Should severe bleeding occur, treatment with Xarelto® must be discontinued and the source of bleeding investigated promptly.** See Other relevant warnings and precautions for concomitant use of drugs affecting hemostasis.

Peri-operative spinal/epidural anesthesia, lumbar puncture: The risk of developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis is increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. Accordingly, the use of Xarelto® at doses greater than 10 mg is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of Xarelto® should be delayed for 24 hours. Patients who have undergone epidural puncture and who are receiving Xarelto® 10 mg should be frequently monitored for signs and symptoms of neurological impairment. If neurological deficits are noted, urgent diagnosis and treatment is necessary. The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use Xarelto® 10 mg only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of Xarelto®. Xarelto® should be administered not earlier than 6 hours after the removal of the catheter. No clinical experience with the use of Xarelto® 15 mg and 20 mg, or Xarelto® 2.5 mg in combination with ASA in these situations.

Renal impairment: Xarelto® must be used with caution in patients with severe renal impairment (CrCl 15-<30 mL/min). Xarelto® should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those concomitantly receiving other drugs which increase rivaroxaban plasma concentrations. Xarelto® is not recommended in patients with CrCl <15 mL/min. Determine estimated creatinine clearance (eCrCl) in all patients before instituting Xarelto®.

Renal impairment (pediatric): No dose adjustment is required for children 1 year or older with mild renal impairment (glomerular filtration rate: 50–80 mL/min/1.73 m^2), based on data in adults and limited data in pediatric patients. Xarelto® is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2), as no clinical data are available. In children younger than 1 year, the renal function should only be determined using serum creatinine. Xarelto® is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Monitoring and laboratory tests: Although Xarelto® therapy will lead to an elevated INR, depending on the timing of the measurement, the INR is not a valid measure to assess the anticoagulant activity of Xarelto®. The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including Xarelto®.

Other relevant warnings and precautions:

- **Information About Excipients:** Xarelto® granules for oral suspension contains 1.8 mg sodium benzoate in each mL oral suspension. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). Xarelto® granules for oral suspension contains less than 1 mmol sodium (23 mg) per milliliter.
- Fall in hemoglobin or blood pressure
- Concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs)
- Chronic concomitant treatment with NSAIDs if receiving Xarelto® 2.5 mg with ASA
- Atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy
- Use of Xarelto® 2.5 mg and ASA in patients with CAD with or without PAD, in combination with or as a replacement for dual antiplatelet therapy (DAPT) or in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE. Not indicated in patients with unstable atherosclerotic disease when DAPT is indicated.
- Use of antiplatelet agents, prasugrel and ticagrelor
- Use of thrombolytics during acute myocardial infarction (AMI) or acute stroke due to expected increased risk of major bleeding
- Patients with prosthetic heart valves, or other valve procedures, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. Not indicated for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement.
- Patients diagnosed with antiphospholipid syndrome and with a history of thrombosis
- Patients with atrial fibrillation who undergo PCI with stent placement
- CAD/PAD patients with history of previous hemorrhagic or lacunar stroke
- CAD/PAD patients in the first month after an ischemic, non-lacunar stroke
- Interaction with strong inhibitors of both CYP 3A4 and P-gp, such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir. These drugs may increase Xarelto® plasma concentrations which increases bleeding risk.
- Dronedarone should not be used concomitantly with rivaroxaban since it may increase exposure of rivaroxaban through P-gp and CYP3A4 inhibition, and thereby the risk of bleeding.
- Patients with mild and moderate renal impairment concomitantly treated with combined P-gp and moderate CYP 3A4 inhibitors such as erythromycin increased exposure to rivaroxaban. Caution is required.
- Interaction with strong CYP 3A4 inducers, such as rifampicin, and the anticonvulsants, phenytoin, carbamazepine, phenobarbital
- Patients with hepatic impairment
- Patients who undergo surgery or invasive procedures including fracture-related surgery of the lower limbs (limited clinical data), pre-operative phase (associated with risk of bleeding) and peri-operative phase when neuraxial (epidural/spinal) anesthesia or spinal puncture is performed (associated with risk of epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis) and post-procedural period (to avoid unnecessary increased risk of thrombosis)
- Patients with lactose sensitivity
- Use of Xarelto® 2.5 mg BID + ASA in patients with chronic CAD with or without PAD or in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE who are ≥75 years of age

For more information:

Please consult the Xarelto® Product Monograph at www.bayer.ca/omr/online/xarelto-pm-en.pdf for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-265-7382.

References: 1. Xarelto® (rivaroxaban) Product Monograph. Bayer Inc. January 6, 2021.
2. Eikelboom JW *et al. NEJM* 2017;377(14):1319–30.

PP-XAR-CA-0888-1

Xarelto® rivaroxaban tablet