OPINION ON MEDICINAL PRODUCTS

rivaroxaban

XARELTO 2,5 mg,

tablet

Registration

Adopted by the Transparency Committee on 21 September 2022

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SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement of XARELTO 2.5 mg (rivaroxaban) for the prevention of atherothrombotic events, in combination with acetylsalicylic acid, **only in adult patients with severe obliterating arteriopathy of the lower limbs (OALL) who have recently undergone a successful surgical or endovascular lower limb revascularisation procedure,** for whom XARELTO 2.5 mg (rivaroxaban) is initiated within 10 days of revascularisation.

Disapproval of reimbursement in other clinical marketing authorisation situations.

Therapeutic improvement?

No progress in the therapeutic strategy for the prevention of atherothrombotic events in adult patients with severe obliterating arteriopathy of the lower limbs (OALL) who have recently undergone a successful lower limb revascularisation procedure.

Role in therapeutic strategy?

The management of stable coronary artery disease and peripheral arterial disease focuses primarily on reducing symptoms and preventing future cardiovascular events, including death. This is based on the management of the patient's lifestyle and on the control of risk factors, in particular through medication.

In chronic coronary syndrome (coronary artery disease), secondary prevention drug treatment includes a combination of antithrombotic agents, lipid-lowering drugs, ACE inhibitors or angiotensin-2 receptor blockers (ARBs). Antithrombotic treatment is tailored to the individual coronary patient according to ischaemic risk, bleeding risk and the clinical context. In patients in sinus rhythm with a history of infarction or myocardial revascularisation:

- low-dose aspirin (75-100 mg per day) is recommended;
- clopidogrel is recommended as an alternative to aspirin in cases of aspirin intolerance (off-label use);
- clopidogrel may be preferred to aspirin in patients with peripheral arterial disease (symptomatic or otherwise), and in those with a history of ischaemic stroke or transient ischaemic attack.

In patients at high or moderate risk of ischaemia, the combination of a second antithrombotic agent (antiplatelet agent or direct oral anticoagulant) with aspirin for long-term secondary prevention should be considered in patients at high risk of ischaemic events and in the absence of a high risk of bleeding.

In symptomatic peripheral arterial disease (PAD) for the secondary prevention of atherothrombotic events, an antiplatelet agent is indicated in patients with symptomatic PAD or who have undergone a revascularisation procedure. In obliterative arterial disease of the lower limbs (OALL) – the most common PAD – various national and international guidelines recommend long-term antiplatelet therapy with aspirin (75 to 325 mg/day) or clopidogrel (75 mg/day) in symptomatic patients (grade IA). This treatment is also recommended for patients who have undergone revascularisation. After percutaneous peripheral revascularisation with stenting, dual therapy with low-dose aspirin and clopidogrel is recommended for 1 month. Thereafter, because of the arterial disease and the high cardiovascular risk, anti-platelet therapy (aspirin or clopidogrel) is continued on a long-term basis.

In patients with a stent for non-atheromatous causes, no recommendations have been established.

In the case of asymptomatic OALL, there is no indication for prescribing an antiplatelet agent as a first-line treatment.

Role of the medicinal product

As a reminder, based on the results of the COMPASS study, the Committee deemed that XARELTO 2.5 mg (rivaroxaban) had no place in the therapeutic strategy for the secondary prevention of atherothrombotic events in patients with coronary artery disease and/or peripheral arterial disease at high risk of ischaemic events (see Committee opinion of 9 October 2019).

Based on the results of the new VOYAGER-PAD study evaluating XARELTO 2.5 mg (rivaroxaban) in combination with acetylsalicylic acid versus acetylsalicylic acid alone, with or without clopidogrel, in adult patients with severe OALL who have recently undergone a successful lower extremity revascularisation procedure, including:

- the modest benefit of adding XARELTO 2.5 mg (rivaroxaban) to antiplatelet therapy in terms of reduction of ischaemic events, mainly due to a reduction of acute lower limb ischaemia, with no gain in mortality over a median follow-up time of 28 months;
- uncertainty about a possible excess risk of cardiovascular death with rivaroxaban 2.5 mg in patients who have undergone endovascular revascularisation, not suggested by the data for patients who have undergone surgical revascularisation;

- the associated increased risk of major and non-major bleeding events, but without an increased risk of fatal or intracranial bleeding;

The Committee deems that the prescription of XARELTO 2.5 mg (rivaroxaban), for the secondary prevention of atherothrombotic events , may be considered **only for adult patients with severe OALL who have recently undergone successful surgical or endovascular lower limb revascularisation,** and **only if** the clinician judges the risk/benefit balance of this treatment to be favourable.

If dual antiplatelet therapy combining clopidogrel and acetylsalicylic acid is warranted, it should be short term (53.0% of patients in the VOYAGER-PAD study received basic treatment with clopidogrel for a median of 31 days).

No studies have yet been conducted to assess the benefit of the rivaroxaban 2.5 mg/acetylsalicylic acid combination compared to clopidogrel alone, another antiplatelet agent recommended for long-term use after revascularisation in patients with severe OALL.

XARELTO 2.5 mg (rivaroxaban) should not be used in patients who have recently undergone revascularisation procedures and are already receiving dual antiplatelet therapy due to a history of stroke or TIA, as they were not evaluated in the VOYAGER-PAD study.

The Committee wishes to emphasise the importance of regular reassessment of prolonged anticoagulant therapy to take into account any new clinical evidence that may call into question the appropriateness of its continuation. The duration of treatment will be determined on a case-by-case basis for each patient, taking into account the risk of thrombotic events versus the risk of bleeding. It should be noted that to date, there is no data documenting the value of maintaining rivaroxaban 2.5 mg beyond three years of treatment (median follow-up time of 28 months in VOYAGER-PAD).

XARELTO 2.5 mg (rivaroxaban) has no place in the prevention of atherothrombotic events in adult patients with symptomatic coronary artery disease at high risk of ischaemic events.

Special recommendations

➔ **Special requests inherent to funding**

Considering:

- the modest effect size of rivaroxaban and acetylsalicylic acid combination therapy compared to acetylsalicylic acid monotherapy;
- the increased risk of bleeding associated with the intensification of antithrombotic therapy;
- difficulties in identifying patients who may benefit from this strategy;

the Committee recommends that the decision to initiate treatment with XARELTO 2.5 mg (rivaroxaban) after revascularisation of the lower limb in patients with severe OALL should be reserved for doctors specialising in cardiology, vascular medicine, vascular surgery or anaesthesia and intensive care.

➔ **Other requests**

The Committee wishes to emphasise the importance of regular reassessment of prolonged anticoagulant therapy to take into account any new clinical evidence that may call into question the appropriateness of its continuation.

Committee's conclusions

Clinical Benefit

- Coronary artery disease and symptomatic peripheral arterial disease are serious conditions with significant morbidity and mortality from major cardiovascular events.
- XARELTO 2.5 mg (rivaroxaban), in combination with aspirin, is a preventive treatment (secondary prevention).
- The efficacy/adverse effect ratio of XARELTO 2 .5 mg (rivaroxaban) in coronary artery disease and symptomatic peripheral arterial disease is currently poorly established:
  - evidence of a modest effect size of rivaroxaban in addition to aspirin compared to aspirin alone was found in the VOYAGER-PAD study only for the prevention of major ischaemic vascular events, with a 2.3% absolute reduction in the risk of occurrence in adult patients with severe obliterative arterial disease of the lower limbs (OALL) who had recently undergone a successful lower limb revascularization procedure (HR=0.85; IC 95% [0.76; 0.96]);
  - and furthermore, there is uncertainty concerning a possible increased risk of cardiovascular death in patients who have undergone endovascular revascularisation ($p_{interaction}$=0.0038), and a higher incidence of minor and major bleeding overall in the rivaroxaban group compared to the placebo group (the incidence of and difference between the groups in terms of major bleeding appeared to be lower according to the TIMI scale (1,9 % for rivaroxaban versus 1.4 % for placebo), used as the main safety criterion in VOYAGER-PAD, than according to the ISTH scale (4.3 % versus 3.1 %), used as the main safety criterion in the COMPASS study.)
- Existence of alternatives: for the prevention of atherothrombotic events in patients with severe OALL, clopidogrel and low-dose aspirin are the conventional treatments.
- The Committee deems that the initial prescription of XARELTO 2.5 mg (rivaroxaban), for the secondary prevention of atherothrombotic events, may be considered in adult patients with severe OALL who have recently undergone a successful surgical or endovascular lower limb revascularisation procedure, **only if** the clinician judges that the benefit/risk balance of this treatment is favourable.

➔ Public health benefit

Considering:

- the severity of coronary artery disease and symptomatic peripheral arterial disease,
- their high prevalence,
- the partially met medical need,
- the modest benefit in terms of reducing ischaemic events, at the cost of an increase in severe bleeding, without evidence of a gain in mortality, **only** in adult patients with severe OALL who have recently undergone a successful lower limb revascularisation procedure,
- the absence of a proven impact on quality of life or delivery of care,

XARELTO 2.5 mg (rivaroxaban) is not likely to have a public health benefit.

Considering all these elements, the Committee deems that the clinical benefit of XARELTO 2.5 mg (rivaroxaban), in combination with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with symptomatic coronary artery disease (CAD) or symptomatic peripheral arterial disease at high risk of ischaemic events is:

- **LOW only for adult patients with severe obliterative arteriopathy of the lower limbs (OALL) who have recently undergone a successful surgical or endovascular lower limb revascularisation procedure and for whom XARELTO 2.5 mg (rivaroxaban) is initiated within 10 days of revascularisation;**
- **INSUFFICIENT in the other clinical marketing authorisation situations of the MA to justify public funding.**

The Committee approves the inclusion of XARELTO 2.5 mg (rivaroxaban) in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary medicinal products approved for community use for the prevention of atherothrombotic events, in combination with acetylsalicylic acid (ASA), only for adult patients with severe obliterating arteriopathy of the lower limbs (OALL) who have recently undergone successful lower limb surgical or endovascular revascularisation, and for whom XARELTO 2.5 mg (rivaroxaban) is initiated within 10 days of revascularisation and at the marketing authorisation doses.

The Committee disapproves the inclusion of XARELTO 2.5 mg (rivaroxaban) in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary medicinal products approved for community use in the other clinical marketing authorisation situations.

Proposed reimbursement rate: 15%

Clinical Added Value

For the prevention of atherothrombotic events, in combination with acetylsalicylic acid, in adult patients with severe obliterating arteriopathy of the lower limbs (OALL) who have recently undergone a successful surgical or endovascular lower limb revascularisation procedure, for whom XARELTO 2.5 mg (rivaroxaban) is initiated within 10 days of revascularisation:

Considering:

- the modest effect size of rivaroxaban 2.5 mg in the VOYAGER-PAD study, in addition to acetylsalicylic acid, compared to acetylsalicylic acid alone, for the prevention of major ischaemic vascular events, with an absolute reduction in the risk of major ischaemic vascular events of 2.3% (15.5% versus 17.8%; HR=0.85; 95% CI [0.76; 0.96], p=0.0085);
- that the benefit of rivaroxaban is not clearly established for the prevention of major ischaemic vascular events other than those affecting peripheral arteries, with the effect of rivaroxaban being mainly attributable to the reduction of acute lower limb ischaemia, with no evidence of benefit for the occurrence of cardiovascular deaths (HR=1.14, IC95% [0.93 ;1.40]) or for all-cause mortality;
- a higher number of major bleeding events in the rivaroxaban group, but no increase in fatal or intracranial bleeding compared to aspirin alone;
- the absence of a study comparing this strategy to clopidogrel alone, another antiplatelet agent recommended for long-term use in this population,

the Transparency Committee deems that XARELTO 2.5 mg (rivaroxaban), in combination with acetylsalicylic acid, provides no improvement in clinical added value (CAV V) in the strategy to prevent atherothrombotic events in adult patients with severe obliterating arteriopathy of the lower limbs (OALL) who have recently undergone a successful lower limb revascularisation procedure.