HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
New indication
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TRANSPARENCY COMMITTEE OPINION SUMMARY

XARELTO 10 mg (rivaroxaban), direct-acting oral anticoagulant

High clinical benefit in the extended prevention of recurrent deep vein thrombosis and pulmonary embolism following completion of at least 6 months of initial anticoagulant therapy but no demonstrated clinical added value in the therapeutic strategy

Main points

- XARELTO 10 mg has a marketing authorisation for the extended prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), following completion of at least 6 months of initial anticoagulant therapy.
- Its benefit has been demonstrated *versus* acetylsalicylic acid in patients with a moderate risk of recurrent thromboembolism in the absence of a high bleeding risk. No data are available for additional treatment durations of more than one year.
- Questions remain concerning identification of those patients who may benefit from extended anticoagulant therapy and the optimal duration of such therapy.
- In extended prevention, the SPC now restricts the use of the 20 mg dosage of rivaroxaban to patients in whom the risk of recurrent DVT or PE is judged to be high. No robust data are available enabling assessment of the difference in effect size between the two dosages relative to the risk of recurrent venous thromboembolism and the bleeding risk.

Pre-existing indications*

XARELTO 10 mg already has a marketing authorisation for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Therapeutic strategy

- The optimal initial anticoagulant therapy duration, generally between 3 and 12 months, should be tailored to the context in which the initial event occurred and the patient's characteristics. Extended anticoagulant therapy is recommended in patients with the highest risk of recurrent VTE (e.g.: idiopathic VTE, recurrent VTE), in the absence of a high bleeding risk; the recommendations remain unclear with respect to the optimum duration of therapy.
- When extended anticoagulant therapy is envisaged, vitamin K antagonists (VKAs), ELIQUIS (apixaban) 2.5 mg and XARELTO (rivaroxaban) 20 mg can be prescribed. The benefit of apixaban 2.5 mg and that of rivaroxaban 20 mg have been assessed *versus* placebo for an additional treatment duration of 12 months following initial therapy for 3 to 12 months, mainly in patients with a low bleeding risk. There are insufficient data available to be able to compare different oral anticoagulant therapies (VKAs and DOACs) with one another in the extended prevention of recurrences.
- The criteria for selection of those patients who may benefit from this strategy are not clearly defined and the available data do not allow any conclusion to be reached concerning the optimal treatment duration. The risk of recurrent VTE is multifactorial, sometimes combining persistent risk factors and transient risk factors that may evolve over time. The decision to continue anticoagulant therapy, as well as the treatment duration and the choice of anticoagulant used should therefore be considered on a case-by-case basis following assessment of the expected benefit in terms of reduction in the risk of recurrence compared to the bleeding risk, also taking into

* This summary does not concern these indications.

account the patient's preferences. If the continuation of therapy seems to be relevant, a switch from an initial therapy that is effective and well tolerated to another oral anticoagulant is not justified.

- The benefit of continuing extended anticoagulant therapy should be regularly reassessed – at last annually – in order to take into account any new factors liable to affect the relevance of maintaining it.

Role of the medicinal product in the therapeutic strategy

- XARELTO 10 mg is a first-line treatment option when extended anticoagulant therapy is envisaged following completion of at least 6 months of initial anticoagulant therapy. Its benefit was demonstrated versus acetylsalicylic acid 100 mg in patients with a moderate risk of thromboembolism who did not have a high bleeding risk. No data are available for additional treatment durations of more than one year.
- In the absence of methodologically acceptable data enabling assessment of the difference in effect size between the two rivaroxaban dosages (10 and 20 mg) with respect to the risk of recurrent venous thromboembolism and the bleeding risk, particularly in patients for whom the risk of recurrent DVT or PE is judged to be high, the respective roles of these two dosages on the basis of patient profile cannot be defined.
  The choice between the 10 mg dosage and the 20 mg dosage, along with the optimal treatment duration, must be left to the practitioner's discretion, following an in-depth individual assessment of the expected benefit in terms of the reduction in the risk of recurrence compared to the bleeding risk.
  The available data do not enable the position of rivaroxaban 10 mg to be determined compared to the other oral anticoagulants available in extended prevention.

Clinical data

- Rivaroxaban 10 mg was assessed in a study comparing rivaroxaban 20 mg/d and 10 mg/d with acetylsalicylic acid (ASA) 100 mg/d, in 3,365 patients having already received anticoagulant therapy for 6 to 12 months following a symptomatic episode of PE or DVT, with no obvious indication for continued therapy. The additional treatment was given for a maximum of 12 months, immediately following the initial therapy.
  The median anticoagulant therapy duration before the study was 7.1 months, and during the study it was 9.5 months. The total anticoagulant therapy duration was between 18 and 23 months for almost half of the patients and more than 24 months for 7.4%.
- The incidence of symptomatic DVT or PE recurrences, fatal or otherwise, was lower during treatment with rivaroxaban 20 mg and 10 mg than with ASA 100 mg, with, respectively:
  - 1.5% in the rivaroxaban 20 mg group compared to 4.4% in the ASA group (HR=0.34; 95% CI [0.20; 0.59], p<0.0001);
  - 1.2% in the rivaroxaban 10 mg group compared to 4.4% in the ASA group (HR=0.26; 95% CI [0.14; 0.47], p<0.0001).
- The incidence of major bleeding was low in the various groups. The overall incidence of confirmed bleeding, all types combined, was higher in the rivaroxaban 20 mg group than in the rivaroxaban 10 mg and ASA 100 mg groups (17.0% versus 13.4% and 12.2% respectively).
- The net clinical benefit, assessed for exploratory purposes using a composite of the primary efficacy outcome plus major bleeding events, was shown to be in favour of rivaroxaban 10 mg compared to ASA (1.5% versus 4.7%; HR = 0.32; 95% CI [0.18-0.55]). The results were similar for the comparison between rivaroxaban 20 mg and ASA.
- As a reminder, a study has already assessed the benefit of rivaroxaban 20 mg in the extended prevention of recurrent DVT and PE following completion of 6 to 12 months of initial therapy, also in patients with no indication to continue anticoagulant therapy. This study demonstrated the superiority of rivaroxaban 20 mg compared to placebo to reduce the recurrent VTE risk, with a major bleeding risk of 0.7% and 0%, respectively. The populations included in these 2 studies were not superimposable.
- The choice of acetylsalicylic acid as a comparator is debatable, since it does not have a marketing authorisation in the treatment of DVT/PE and the prevention of recurrence, in contrast with VKAs or apixaban. The effect size and study design do not enable demonstration of the non-inferiority of low-dose rivaroxaban (10 mg) compared to rivaroxaban at the full dose (20 mg), particularly in subgroups of patients at high risk of recurrence. Yet a major objective is to determine whether, in patients at high risk of recurrence, such as those with an unprovoked first episode of venous thromboembolism (VTE) or, particularly, unprovoked recurrent VTE or VTE associated with a persistent factor, low-dose rivaroxaban (10 mg) is non-inferior in terms of the risk of recurrent venous thromboembolism and superior in terms of the bleeding risk compared to rivaroxaban continued at the full dose (20 mg).
  The additional anticoagulant therapy duration in the context of the study was short compared to the theoretical indication for long-term anticoagulant therapy, potentially without any predefined discontinuation date. Patients in whom the continuation of anticoagulant treatment at a therapeutic dose was indicated beyond the initial treatment duration of 6 to 12 months were excluded from the study, without being defined. The factors having prompted the decision to extend treatment beyond the duration of 6 or 12 months are not known. The population studied had a moderate risk of thromboembolic recurrence, with 60% of patients included having a concomitant factor provoking the VTE, not theoretically the target population for extended treatment following the completion of 6

months of initial therapy. The transposability of the results to an older population, with impaired renal function and/or a higher bleeding risk is not guaranteed. It is also difficult to transpose the results to cancer patients due to their low representativeness in the study.

- In the absence of comparisons with the anticoagulant therapies already available, the impact of rivaroxaban 10 mg on morbidity and mortality or on quality of life in this indication is not currently demonstrated.

Benefit of the medicinal product

- The actual clinical benefit* of XARELTO 10 mg is high.
- XARELTO 10 mg does not provide any clinical added value** (CAV V) in the strategy for the extended prevention of recurrent DVT and PE following completion of 6 months of initial anticoagulant therapy.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 17 October 2018 (CT-16810) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".