HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
2 JUNE 2021

rivaroxaban

XARELTO 15 mg and 20 mg film-coated tablets
Indication extension

XARELTO 1 mg/mL granules for oral suspension
Inclusion in list

Key points

Favourable opinion for reimbursement in the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in the paediatric population after at least 5 days of initial parenteral anticoagulation treatment. (for more details, see MA).

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The objective of paediatric VTE management is to:

- treat venous thromboembolism and prevent early and late recurrence,
- prevent the progression of the thrombotic event (such as pulmonary embolism), complications (such as post-thrombotic syndrome) and mortality,
-
- and preserve the central venous capital of children with chronic illnesses.

In haemodynamically stable children, initial treatment with a parenteral anticoagulant is recommended, with rapid initiation. This treatment is based on low molecular weight heparin (LMWH by the SC route) and/or unfractionated heparin (UFH by the SC or IV route). Fondaparinux (SC route) is administered in some countries, but it is not widely used internationally.

Anticoagulant treatment can then be continued using LMWH or vitamin K antagonist therapy (oral VKA therapy), with a treatment duration defined on a case-by-case basis depending on the clinical situation, the patient's age, and following assessment of the benefit compared to the bleeding risk.

The recommended treatment durations are 3 months in the event of provoked thrombosis if the transient risk factor is resolved; otherwise, anticoagulant therapy should be continued for as long as the risk factor persists. In the event of unprovoked thrombosis, the treatment duration is 6 to 12 months. The period is indefinite in the event of recurrent unprovoked thrombosis.

In children with catheter-related VTE, the guidelines suggest leaving central venous access devices or umbilical catheters in place if they are clinically necessary or functional, and initiating anticoagulant therapy. If they are no longer functional or clinically necessary, it is recommended that they be removed after 3 to 5 days of anticoagulant therapy. Initial anticoagulant therapy is based on LMWH or UFH followed by LMWH, with a total treatment duration of between 6 weeks and 3 months.

The parenteral anticoagulant therapies currently available are not authorised in France for paediatric use. In addition, the use of the recommended treatments is not entirely suitable for the paediatric population, since they require repeated injections and/or regular laboratory monitoring, particularly with VKAs (numerous interactions with other medicinal products and foods, intercurrent infections, leading to variations in INR). Only the proprietary medicinal product WARFARIN 1 mg/mL oral suspension is available in a delivery form appropriate for young children via a named-patient compassionate use programme (ATU). Heparins and VKAs now have a reversal agent.

Two DOACs have an MA in VTE in the paediatric population: XARELTO (rivaroxaban) since January 2021, which is the subject of the current assessment, and PRADAXA (dabigatran) since January 2021. It should be noted that the pharmaceutical company marketing PRADAXA (dabigatran) has not applied for reimbursement in this indication, for either the tablet form or the oral solution form.

DOACs do not require routine monitoring of anticoagulation or laboratory testing. Although they are less numerous than with VKAs, interactions with other medicinal products are possible and are liable to increase or reduce plasma concentrations (see SPC for XARELTO (rivaroxaban)). No methods are currently available to measure the level of anticoagulation they induce in routine practice. Current routine haemostasis tests do not indicate the level of anticoagulation.

Role of the medicinal product in the care pathway:

In the treatment of venous thromboembolism in the paediatric population, XARELTO (rivaroxaban) proprietary medicinal products can be used following heparin therapy for at least 5 days.

The Committee highlights the utility of having access to this first DOAC in oral solution form, along with the practical benefits of this formulation for paediatric use.

It reiterates that the fact that there is no need to routinely measure the level of anticoagulation under DOACs must not lead to reduced clinical monitoring of these patients.

A reversal agent for rivaroxaban, andexanet alfa, has been authorised since April 2019 for patients presenting potentially fatal or uncontrolled bleeding. On the date of the present opinion, this medicinal product is not available in France and no assessment has been conducted by the Committee.

Special recommendations

Given the bleeding risk and the need for close clinical monitoring of children with venous thromboembolic disease (adjustment of doses and administration frequency based on weight, treatment compliance, reversal in the event of severe bleeding), the Committee recommends initial hospital prescription of XARELTO (rivaroxaban) for the paediatric population, with specific therapeutic patient education delivered by a multidisciplinary team. In addition, in view of the complexity of administration with the oral formulation, the Committee recommends the implementation of a communication plan aimed at healthcare professionals liable to treat these patients, via the formalisation of a prescribing and dispensing guide, for example.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Venous thromboembolic disease is a serious disease that can be life-threatening (potentially fatal pulmonary embolism) or have serious sequelae (post-thrombotic syndrome).

◗ XARELTO (rivaroxaban) proprietary medicinal products are curative treatments for venous thromboembolism and prophylactic therapies to prevent recurrence.

◗ The efficacy/adverse effects ratio is high in this indication.

◗ There are medicinal alternatives.

◗ In the treatment of venous thromboembolism in the paediatric population, XARELTO (rivaroxaban) proprietary medicinal products can be used following heparin therapy for at least 5 days.

Public health impact

Considering:

- the seriousness of the disease and its low incidence,
- the medical need partially met by the currently available alternatives,
- the partial response to the identified need given:
    - the absence of a demonstrated additional impact on morbidity and mortality,
    - an expected, but not demonstrated, impact on the organisation of care and the patient's quality of life, due to the availability of an oral solution formulation appropriate for paediatric patients and an oral medicinal product not requiring laboratory monitoring,

XARELTO (rivaroxaban) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of XARELTO (rivaroxaban) is substantial in the MA indication.
The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:
- **the efficacy data for rivaroxaban derived from a study versus standard-of-care therapies (chosen by the investigator), on the reduction of venous thromboembolism in a paediatric population previously treated with parenteral anticoagulation therapy for at least 5 days, the interpretation of which can only be descriptive (EINSTEIN-Junior), insofar as the study did not include any formulated statistical hypothesis or any sample size calculation,**
- **the absence of robust data on morbidity,**
- **the absence of data on mortality,**
- **the safety profile in the paediatric population similar overall to that in adults,**
- **uncertainties with respect to its efficacy, safety and longer term use in routine practice and in children under the age of 6 years,**

and despite:
- **the potential benefit of having access to a medicinal product with a formulation appropriate for paediatric use and not requiring laboratory testing for monitoring of treatment, in terms of patients' quality of life and care pathway, although this has not been demonstrated,**

the Committee considers that XARELTO (rivaroxaban) provides no clinical added value (CAV V) in the management of venous thromboembolism (VTE) in the paediatric population after at least 5 days of initial parenteral anticoagulation treatment.

The Committee highlights the utility of having access to this first DOAC in oral solution form, along with the practical benefits of this formulation for paediatric use.