Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Medical Care and Sports
PO Box 20350
2500 EJ THE HAGUE

2021004859

National Health Care Institute
Care I

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Dr T.H.L. Tran
T +31 (0)6-12001412

Date 17 March 2021
Subject rivaroxaban (Xarelto®): inclusion of rivaroxaban suspension 1 mg/ml and changes to further conditions for 15 mg and 20 mg tablets

Our reference
2021004859

Dear Ms van Ark,

In your letter of 9 February 2021 (CIBG-21-01418), you asked the National Health Care Institute to carry out a substantive assessment of whether the product rivaroxaban 1 mg/ml suspension can be included.
Additionally, you asked for changes to the further conditions for rivaroxaban 15 mg and 20 mg tablets.
Your request concerns a change to a pre-existing indication for rivaroxaban, so the National Health Care Institute will address this change to the further conditions in the form of a report letter.

Current situation
Rivaroxaban is available as 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. This product has already been included in the Medicine Reimbursement System (GVS) for insured persons aged 18 or older who meet one of the following conditions:

1 who are reliant on this medicine for the prevention of venous thromboembolism after elective knee or hip replacement surgery,
2 have non-valvular atrial fibrillation and one or more risk factors and are using this medicine to prevent cerebrovascular accidents or systemic embolism in accordance with the introduction guide accepted by the relevant physicians association in the Netherlands,
3 are reliant on this medicine in combination with acetylsalicylic acid and clopidogrel for preventive treatment of an acute coronary syndrome with elevated cardiac biomarkers and who have not had a stroke or TIA, or
4 are reliant on this medicine to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrent DVT and PE
5 are reliant on this medicine in combination with acetylsalicylic acid for preventing atherothrombotic events in patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) who are at high risk of ischaemic events.

Rivaroxaban has been included on List 1A in cluster OB01AXBO together with dabigatran, apixaban and edoxaban, with List 2 conditions. The current conditions for rivaroxaban, dabigatran, apixaban and edoxaban are for all

drugs aimed at adults.

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In January 2021, the European Medicines Agency (EMA) approved the following indication for paediatric patients. This registration applies to tablets of 15 mg and 20 mg and the 1 mg/ml suspension:

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in full-term neonates, infants and toddlers, children and adolescents aged less than 18 after at least 5 days of initial parenteral anticoagulation treatment. For the 15 mg tablets, it is stated that the paediatric patient's weight must be 30 kg to 50 kg, and for the 20 mg tablets at least 50 kg.

The marketing authorisation holder is applying for reimbursement for the 15 mg and 20 mg tablets and the 1 mg/ml suspension.
VTE is an umbrella term that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). For that reason, as regards the 15 mg and 20 mg tablets, this is about an extension to the indication of the licensed indication: "Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrent DVT and PE in adults".

Rivaroxaban dosage
Treatment of children and adolescents aged less than 18 with rivaroxaban should be started after initial parenteral anticoagulation treatment lasting at least five days. The dose for children and adolescents is calculated based on bodyweight. For the dosage regime, please refer to the summary of product characteristics (SmPC)[1]

Outcome for therapeutic value
See the annex for the description of the study.
Based on the data in the annex, the National Health Care Institute has concluded that rivaroxaban has therapeutic added value when treating VTE in children compared to the standard treatment (low molecular weight heparin and vitamin K antagonists).

Outcome of the budget impact analysis
See the annex for the budget impact analysis.
The total budget impact, without taking account of the substitution of low molecular weight heparin and vitamin K antagonists, is €41,833 in year three after inclusion in the health care package.

Advice from the National Health Care Institute
Rivaroxaban in doses of 15 mg and 20 mg has already been included on List 1A with further conditions for adults. Based on the considerations mentioned above, the National Health Care Institute advises that you should modify the List 2 conditions for rivaroxaban by adding the condition for children, as set out below.
Extension with these further conditions will involve additional costs. The National Health Care Institute is aware that there is currently a financial arrangement for rivaroxaban.
Because dabigatran, apixaban and edoxaban are not licensed for children, the National Health Care Institute advises that you should not change the conditions for these drugs, which rivaroxaban is clustered with.

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Rivaroxaban suspension 1 mg/ml has not yet been included in the Medicine Reimbursement System. The licensed indication for this formulation is only limited to use in children. Based on the cluster criteria, the National Health Care Institute advises that rivaroxaban suspension 1 mg/ml should be included on List 1B.

Extension of further conditions for rivaroxaban 15 mg and 20 mg for VTE

Conditions for rivaroxaban
For insured persons of 18 or older:

1. who are reliant on this medicine for the prevention of venous thromboembolism after elective knee or hip replacement surgery,
2. have non-valvular atrial fibrillation and one or more risk factors and are using this medicine to prevent cerebrovascular accidents or systemic embolism in accordance with the introduction guide accepted by the relevant physicians association in the Netherlands,
3. are reliant on this medicine in combination with acetylsalicylic acid and clopidogrel for preventive treatment of an acute coronary syndrome with elevated cardiac biomarkers and who have not had a stroke or TIA, or
4. are reliant on this medicine to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrent DVT and PE
5. are reliant on this medicine in combination with acetylsalicylic acid for preventing atherothrombotic events in patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) who are at high risk of ischaemic events.

Or, for insured full-term neonates, infants and toddlers, children and adolescents aged less than 18:
1 who are reliant on this medicine for the treatment of venous thromboembolism (VTE) and the prevention of VTE recurrence after at least 5 days of initial parenteral anticoagulation treatment

Further condition for rivaroxaban suspension 1 mg/ml
Condition for rivaroxaban suspension 1 mg/ml
For insured full-term neonates, infants and toddlers, children and adolescents aged less than 18:
1 who are reliant on this medicine for the treatment of venous thromboembolism (VTE) and the prevention of VTE recurrence after at least 5 days of initial parenteral anticoagulation treatment

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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Assessment for the extension of the indication VTE in children

Rivaroxaban is licensed for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18after at least 5 days of initial parenteral anticoagulation treatment.[1] This indication has not been assessed by the National Health Care Institute before.

Venous thromboembolism in children

Venous thromboembolism is an umbrella term that includes both deep vein thrombosis and pulmonary embolism. A retrospective study from 2001 found that over 1 in 100,000 children in the Netherlands are diagnosed with VTE every year.[2] The Dutch Thrombosis Foundation reported that around 350 babies and children get thrombosis every year[3]. About half of the diagnosed patients are neonates.[2]

A distinction is made between idiopathic VTE (with no known cause) or VTE where there is a risk factor[4]. The most important risk factor in neonates is the use of a central venous catheter (94%). In children, the risk factors for VTE vary; some of the most frequently mentioned are infections (45%), central venous catheters (37%), heart diseases (19%), immobility (17%) or surgery (15%).[2] In a previous study into the treatment of VTE in children (the REVIVE study), it was found that 97% of these children had severe underlying conditions, including malignancy (29.5%), infection (11.5%), congenital heart disease (9%), a gastrointestinal disorder (7.7%) or immune disorders (7.7%).[5]

The symptoms depend on the location of the thrombosis. Symptoms of thrombosis in the upper half of the body (which is usually catheter-related) are thrombocytopenia, failure or malfunction of the catheter, persistent sepsis, arrhythmia, superior vena cava syndrome or haemodynamic problems. Pulmonary embolisms cause symptoms of dyspnoea, chest pain during breathing, an unexplained need for oxygen and not being able to be weaned from mechanical ventilation. Mortality resulting from thromboses among children is about 1-4%. Recurrent thromboses occur in 5.6% to 11% of children.[6]

Treatment guideline for VTE in children

The treatment of VTE in paediatric patients is described in the 'Protocol for diagnosis and treatment of venous thromboembolism in children' of the Dutch Paediatric Association (NVK, translated title).[6]

Treatment options

The NVK protocol recommends treating thromboses in children with heparin (low molecular weight heparin/LMWH) or unfractionated heparin), followed by LMWH or vitamin K antagonists. The vitamin K antagonists used in the Netherlands are acenocoumarol or phenprocoumon. For treating venous thromboembolism in children, the target value for the international normalised ratio (INR) is 2.5 to 3.5, with a therapeutic lower limit of 2.0. The LMWHs used are nadroparin, enoxaparin, dalteparin or tinzaparin.[6]

The duration of the anticoagulation therapy is 3 months for non-persistent risk factors and 6 months for idiopathic thrombosis. Where there is a persistent risk factor, it is recommended to continue anticoagulation at prophylactic or therapeutic doses (depending on the risk factor) until the risk factor is no longer present. Recurrent thromboses are treated for an indefinite period. The duration

of treatment is determined for the individual patient and depends on the balance between the risk of thrombosis and the risk of haemorrhage and is assessed regularly. Prophylactic doses of anticoagulation therapy can be considered if necessary[6]. In infants, LMWH is preferred to vitamin K antagonists as follow-up treatment[6].

Study data
The European Medicines Agency has recently described the effectiveness of rivaroxaban in paediatric patients in a European Assessment Report[7]. The principal study underpinning the extension to the indication is the study NCT02234843, also known as the EINSTEIN junior study[8]. It is a multicentre, open-label, randomised study in which children were randomised after an initial treatment with heparin lasting at least 5 days to either treatment with a bodyweight-adjusted dose of rivaroxaban (in the form of a tablet or suspension) or standard anticoagulants (heparin (either unfractionated or converted to LMWH), fondaparinux or a vitamin K antagonist). Children were initially treated for 3 months, except for children aged < 2 years with catheter-related VTEs, which were treated for 1 month. After that initial duration of treatment, a decision was made as to whether it needed to be extended. The primary outcome measure was the number of symptomatic recurrent VTE. A secondary outcome measure was the composite of symptomatic recurrent VTE and asymptomatic exacerbation of the thrombotic condition on repeated imaging. For the unfavourable effects, the key outcome measure was a composite endpoint of severe (major) bleeding and non-severe clinically relevant bleeding. The assessment of the outcome measures was done by an independent review committee.
A total of 335 patients were randomised to treatment with rivaroxaban and 165 patients to the control arm. 276 children were 12 to < 18 years, 101 children were 6 to < 12 years, 69 were 2 to < 6 years and 54 were < 2 years.

Desirable effects
Symptomatic recurrent VTE occurred in 1.2% (4 out of 335) patients in the rivaroxaban arm and 3.0% (5 out of 165) patients in the control arm. The secondary outcome measure, the composite endpoint of symptomatic recurrent VTE and asymptomatic exacerbation of the thrombotic condition, occurred in 1.5% (5 out of 335) patients in the rivaroxaban arm and 3.6% (6 out of 165) patients in the control arm.
Repeated imaging showed that the thrombus had dissolved in 38.2% (128 patients) in the rivaroxaban arm and 26.1% (43 patients) in the control arm.

Undesirable effects
Severe (major) bleeding and non-severe clinically relevant bleeding occurred in 10 children (3%) in the rivaroxaban group and in 3 children (2%) in the control arm. Severe bleeding (major haemorrhages) occurred in none of the patients in the rivaroxaban arm and in two patients in the control arm.
The most common undesirable effects that occurred during the treatment were headache (17%), epistaxis (11%), vomiting (11%) and fever (10%) for rivaroxaban and headache (15%) and epistaxis (11%) in the control arm.
Treatment-related undesirable effects occurred in 90 of the 329 patients (27%) in the rivaroxaban arm and 27 of the 162 patients (17%) in the control arm. In 4 (1%) of patients in the rivaroxaban arm and 2 (1.2%) of patients in the control arm these undesirable effects were defined as severe. A total of 11 patients (3%) discontinued rivaroxaban as the result of an undesirable effect. In the control

arm, 3 patients (2%) discontinued treatment as the result of an undesirable effect. No patients died as the result of an undesirable effect.

Discussion

Until now, little evidence was available for the treatment of VTE in children. The treatment of VTE in children has previously been researched in the REVIVE study[5] but that study was prematurely stopped owing to slow enrolment of patients. In the EINSTEIN junior study[8], a diverse population of paediatric patients with VTE were included, with a wide variety of underlying conditions. The included population seems comparable to the population of paediatric patients in the Netherlands.

In the control arm of the EINSTEIN junior study, paediatric patients could also be treated with warfarin, fondaparinux and unfractionated heparin after the initial treatment with heparin. These treatments are not listed as follow-up treatment in the NVK protocol, but the other treatment options are in line with the treatment given in the Netherlands. The control treatment does not therefore exactly match the standard treatment in the Netherlands.

One limitation of this study is that it is not powered to demonstrate non-inferiority in comparison with the control treatment. The reason for this is the low incidence of VTE among children and the lack of a known effect in the control arm. For that reason, non-inferiority or superiority in comparison with the control arm could not be demonstrated with this study design.

In general, the effectiveness and safety profile of rivaroxaban was comparable to the safety profile observed in the adult population and consistent across the various age groups. In children aged < 2 years, relatively more bleedings seemed to occur compared to the control treatment (based on a relatively small number of patients). The European Public Assessment Report (EPAR) states that a Scientific Advisory Group (SAG) has indicated that it considered that using rivaroxaban in all paediatric patients is sufficiently supported by the results of the trial. The SAG emphasized the difficulties associated with the standard treatment in terms of administration and monitoring. The SAG's opinion was that the benefits of having an oral preparation available outweigh the small increased risk of bleeding.

The formulation of rivaroxaban makes it easier to use in paediatric patients than vitamin K antagonists or LMWH, given that the dosage is easier to define than for vitamin K antagonists and that oral administration has benefits compared to a subcutaneous injection as used for LMWH. In young children in particular, an oral suspension can offer a solution if taking tablets is unsuitable. Additionally, treatment with rivaroxaban gives relatively fewer interactions with other medicines.

Based on the study design, it is not possible to make any statement about non-inferiority or superiority compared with the control treatment. The results from the rivaroxaban arm of the EINSTEIN junior study seem comparable with the results in adults.

Given that the current standard treatment can be difficult in children in terms of administration and monitoring, the availability of an oral formulation that is easier to dose and needs less monitoring offers added value for paediatric patients.

Conclusion for rivaroxaban in treating VTE in children

To summarise, we have concluded that rivaroxaban has therapeutic added value when treating VTE in children compared to the standard treatment (low molecular weight heparin and vitamin K antagonists).

Budget impact analysis for rivaroxaban

Data from the Dutch thrombosis service shows that 350 children per year get a VTE[5]. This figure comprises 175 neonates (50%) and 175 children and adolescents aged < 18. Children aged < 18 are currently treated with a subcutaneously administered LMWH (low molecular weight heparin) or oral VKA (vitamin K antagonist), with the dose depending on bodyweight. Neonates are treated with a subcutaneously administered LMWH. Based on expert opinion, the following market penetration (as a suspension or tablets) has been estimated for rivaroxaban 3 years after inclusion in the health care package. This takes account of the fact that 60% of neonates cannot be considered for rivaroxaban because their bodyweight is too low (< 2.6 kg).

- 40% of neonates will be treated with rivaroxaban suspension instead of a low molecular weight heparin. 70 neonates will be treated this way.
- 10% of children aged < 18 will be treated with rivaroxaban suspension instead of the standard therapy with LMWHs or VKAs. 18 children will be treated this way.
- 90% of children aged < 18 will be treated with rivaroxaban tablets instead of the standard therapy with LMWHs or VKAs. 157 children will be treated this way.

There are two different packaging formats for the rivaroxaban suspension (suitable for children weighing up to 30 kg): the first is a bottle containing 51.7 mg (1 mg/ml) rivaroxaban costing €10.10 that is enough to treat a new-born or small child for at least 14 days. The daily cost is thus €0.72. The second is a bottle of 103.4 mg (1 mg/ml) rivaroxaban costing €20.20 that is enough to treat a child for at least 10 days. The daily cost is thus €2.02. Furthermore, two tablet dosages are licensed (15 mg and 20 mg); each costs €2.02 per tablet.

The treatment duration is 3 months for about 95% of children aged < 18 and 12 months for about 5% of children aged < 18. All neonates are treated for 3 months. The per-patient costs of rivaroxaban are shown in the table below.

	Neonates	**Children aged <18**			
Administration	Suspension	Suspension	Suspension	Tablet	Tablet
Unit	51.7 mg (1 mg/ml)	103.4 mg (1 mg/ml)	103.4 mg (1 mg/ml)	15 or 20 mg	15 or 20 mg
Costs per day	€0.72	€2.02	€2.02	€2.02	€2.02
Duration of treatment in months[a]	3	3	12	3	12
Costs per treatment	€65.70	€184.33	€737.30	€184.33	€737.30
Percentage of treatment duration	100%	95%	5%	95%	5%
Number of children	70	17	1	149	8
Costs per subgroup	*€4,599*	*€3,133.61*	*€737.30*	*€27,465.17*	*€5,898.40*
Total costs					**€41,833**

[a] 3 months is 91.25 days and 12 months is 365 days

There are two VKA (vitamin K antagonists) and four different LMWHs (low molecular weight heparins) available in the Netherlands but none of them describes a paediatric dosage regimen. The dosage regimen for VKAs is complex because the dose is individualised depending on the INR (international normalised ratio). Because of these restrictions, the savings on VKAs and LMWHs have not been included in this budget impact analyses, meaning that the budgetary impact will have been overestimated.

The total budget impact, without taking account of the substitution of VKAs and LMWHs, thus comes to €41,833 in three years after inclusion in the health care package.

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