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2022005442

Case number
2022004735

Our reference
2022005442

Your reference
CIBG-22-03252

Your letter of
31 January 2022

Date 25 April 2022
Subject GVS advisory report on dabigatran etexilate (Pradaxa®) capsules extension – further conditions

Dear Mr Kuipers,

In your letter of 31 January 2022 (CIBG-22-03252), you asked the National Health Care Institute for advice on the extension of the further conditions for the reimbursement of dabigatran etexilate (Pradaxa®) capsules for a paediatric application.

We will reply to your request in the form of a letter report.

Background
Dabigatran (Pradaxa®) is a direct inhibitor of thrombin and it belongs to the group of Direct Oral AntiCoagulants (DOACs). Other DOACs are rivaroxaban, apixaban and edoxaban. The DOACs have been included on List 1A and List 2 of the Healthcare Insurance Regulations, more specifically in the cluster 0B01AXBO V.

Medicinal products included in cluster 0B01AXBO V*			
ATC code	Generic name	Brand name	Formulation and strength
B01AE07	dabigatran	Pradaxa®	Capsule. 75 mg, 110 mg, 150 mg
B01AF01	rivaroxaban	Xarelto®	Tablet. 2.5 mg, 10 mg, 15 mg, 20 mg
B01AF01	rivaroxaban	Xarelto®	Granules for oral suspension <4 kg. 1 mg/ml Granules for oral suspension ≥4 kg. 1 mg/ml
B01AF02	apixaban	Eliquis®	Tablet. 2.5 mg, 5 mg
B01AF03	edoxaban	Lixiana®	Tablet. 15 mg, 30 mg , 60 mg
* Various conditions for List 2 apply to these DOACs.			

The further conditions for dabigatran have been included – along with those for apixaban – in Section 101 of List 2. They read as follows:
101. Dabigatran and apixaban
Condition:
only for insured persons aged eighteen or older
a. who are reliant on this medicine for the prevention of venous

thromboembolism after elective knee or hip replacement surgery,

b. *with non-valvular atrial fibrillation and one or more risk factors and using this medicine to prevent cerebrovascular accidents or systemic embolism in accordance with the introduction guide accepted by the relevant professional groups in the Netherlands, or*
c. *reliant on this medicine to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrent DVT and PE.*

Although the current reimbursement conditions for the various DOACs focus on adults, the conditions for rivaroxaban (following an extension of the licensed indication and subsequent assessment by the National Health Care Institute) have recently been extended for paediatric use. [I] [II]

Dabigatran is the second DOAC to receive approval for paediatric use from the licensing authority. The marketing authorisation holder claims that dabigatran is therapeutically comparable to rivaroxaban in the treatment of venous thromboembolism (VTE) in children and requests that the further conditions for dabigatran be extended to include that group.

The licensed indications for dabigatran (Pradaxa®) after the extension are:
- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or elective total knee replacement surgery.
- Treatment of VTE and prevention of recurrent VTE in paediatric patients who have not yet reached 18 years of age.[III]

The licence is for the capsules (75, 110 or 150 mg), coated granulate (20, 30, 40, 50, 110 or 150 mg) and powder with solvent for an oral solution (6.25 mg/38 ml). Only the capsule form (for patients aged 8 years or older who can swallow the capsules whole) is available in the Netherlands. Coated granules (for children under 12 years of age) and the oral solution (for children under 1 year of age) containing dabigatran are not marketed in the Netherlands.

The current reimbursement request only relates to dabigatran capsules. Consequently, the applicant's request is limited to the group of patients aged 8 and older. No reimbursement request is being submitted for younger children who cannot swallow the capsules. The applicant proposes extending the further conditions for dabigatran to include the group of insured persons aged 8 to 18 who are reliant on this medicine for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE.

[I] National Health Care Institute, Diemen. 17 March 2021. GVS advisory report on rivaroxaban (Xarelto) extension – further conditions. Available at: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/03/17/gvs-advies-rivaroxaban-xarelto-bij-de-preventie-en-behandeling-van-vte-bij-kinderen.

[II] The further conditions for rivaroxaban tablets (no. 95) and rivaroxaban suspension (no. 129) were amended as of 1 June 2021. The extended indication reads as follows:
Rivaroxaban
Only for insured persons:
1. [….]
2. for full-term neonates, infants and toddlers, children and adolescents aged under 18 who are reliant on this medicine for the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE after anticoagulation treatment lasting at least 5 days.

[III] European Medicines Agency, Amsterdam. 2021. Pradaxa. Summary of product characteristics. Consulted in February 2022 via https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_nl.pdf.

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Outcome for therapeutic value
The assessment of the therapeutic value and the description of the clinical study are described in the appendix.
Based on the data in the appendix, the National Health Care Institute has concluded that dabigatran as treatment of VTE in children aged eight and older has a therapeutic value comparable to the standard treatment (low molecular weight heparin or vitamin K antagonists).

Other considerations
- Although dabigatran is also licensed for patients from birth to less than 18 years of age, no suitable form of administration for the group aged 0-8 years is available on the Dutch market. Rivaroxaban suspension is available for young children (up to 8 years of age) who are eligible for treatment of venous thromboembolism.

Advice from the National Health Care Institute
Dabigatran is already included on List 1A with further conditions for adults. Based on the above considerations, the National Health Care Institute advises amending List 2 of the Healthcare Insurance Regulations. Number 101 can be retained for apixaban. For dabigatran, the new condition can be formulated as given below (in italics). Extension with these further conditions will involve additional costs.

Because 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 dabigatran is clustered with.

Formulation of condition for List 2
140. Dabigatran
Condition:
only for insured persons
1 aged eighteen or older
   a who are reliant on this medicine for the prevention of venous thromboembolism after elective knee or hip replacement surgery,
   b with non-valvular atrial fibrillation and one or more risk factors and using this medicine to prevent cerebrovascular accidents or systemic embolism in accordance with the introduction guide accepted by the relevant professional groups in the Netherlands, or
   c who are reliant on this medicine to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent recurrent DVT and PE, or
2 aged eight to eighteen who are reliant on this medicine for the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE after parenteral anticoagulation treatment lasting at least 5 days.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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APPENDIX

Assessment of therapeutic value

Dabigatran has recently been licensed for treatment of VTE and prevention of recurrent venous thromboembolism (VTE) in paediatric patients who have not yet reached 18 years of age.[1] This new indication for dabigatran has not yet been assessed by the National Health Care Institute.

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' drawn up by the Dutch Association for Paediatric Medicine (NVK).[2]
  The guideline recommends, inter alia, treating venous thrombosis in children with heparin (low molecular weight heparin – LMWH – or unfractionated heparin), followed by LMWH or vitamin K antagonists (VKA: acenocoumarol, fenprocoumon); consider using a DOAC in teenagers and, in teenagers who are on antithrombotic treatment for an indefinite period, converting to 10 mg rivaroxaban once daily after 12 months.
  The guideline also says:
  - Low molecular weight heparin appears to be effective for initial treatment of venous thrombosis in children.
  - For treating venous thrombosis in children, heparin or fondaparinux followed by rivaroxaban is as effective and safe as heparin or fondaparinux followed by vitamin K antagonists.
  - Dabigatran is safe (risk of major haemorrhage 1.5%, risk of recurrent thrombosis 1.0%) for secondary prevention of venous thrombosis in children older than 3 months with persistent risk factors for thrombosis.
- 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; this is assessed regularly.[2]

Study data

The marketing authorisation holder (MAH) claims that dabigatran is therapeutically comparable to rivaroxaban in the treatment of VTE in children. For this application, dabigatran has not been studied in a direct comparison with rivaroxaban; we are therefore forced to make an indirect comparison.

The main study that the indication extension for dabigatran is based on is the DIVERSITY study (Halton et al., 2020),[3] [4] studying the treatment of VTE in children.
Dabigatran for preventing recurrent VTE in children was investigated in the follow-up study to DIVERSITY (Brandão et al., 2020).[5]
Finally, the EINSTEIN junior study (rivaroxaban in children) should be noted.[6] This study has already been discussed in our evaluation report on rivaroxaban.[7]

<u>The DIVERSITY study with dabigatran</u> [4]

This study is an open-label, randomised, phase 2b/3, non-inferiority study with parallel groups comparing dabigatran (with the dose adjusted for age and weight)

directly against the standard treatment (LMWH, unfractionated heparin, vitamin K antagonist or fondaparinux).
A total of 267 children were studied (35 children aged 0 to < 2 years; 64 children aged 2 to < 12; 168 children aged 12 to < 18). These were children with acute venous thromboembolism who were initially treated with parenteral anticoagulation (for 5 to 21 days) and then required oral anticoagulation therapy for at least 3 months.

The primary endpoint for efficacy was a composite endpoint consisting of the proportion of children with complete thrombus resolution and freedom from recurrent VTE and venous thromboembolism-related death.
Adverse effects such as major bleeding events [time-to-event analysis on the treated population set] were investigated as a secondary endpoint.

The key results of the DIVERSITY study are shown below.[4]

	Control group	Intervention group
n/N (%)	90/267 (34%)	77/267 (66%)
Treatment n/N (%)	Standard treatment • VKA 49/90 (54%) • LMWH 40/90 (44%) • Fondaparinux 1/90 (1%)	Dabigatran 177/177 (100%)
median exposure	85.0 days (IQR 80.0 to 90.0)	85.5 days (IQR 78.0 to 89.0)
1st outcome measure (composite)	38/90 (42%)	81/177 (46%)
	Mantel-Haenszel weighted difference: −0.04; 90%CI: −0.14 to 0.07; p<0.0001 for non-inferiority (margin 20%). As per the protocol, superiority was tested in the case of non-inferiority (i.e. whether dabigatran is better than the standard treatment). This was not demonstrated (p=0.27).	
• Complete thrombus resolution	38 (42%)	81 (46%)
• Freedom from recurrent VTE	83 (92%)	170 (96%)
• Freedom from VTE-related mortality	89 (99%)‡	177 (100%)
On-treatment bleeding events	22/90 (24%)	38/176 (22%)
	Hazard ratio [HR] 1.15; 95% CI: 0.68 to 1.94; p=0.61 (not significant)	
major bleeding events*	2/90 (2%)	4/176 (2%)
	HR 0.94; 95% CI: 0.17 to 5.16; p=0.95 (not significant)	
SAEs (serious adverse events)	18/90 (20%)	22/176 (13%)
• Vascular disorders	3/90 (3%)	2/176 (1%)
• Gastrointestinal side-effects	2/90 (2%)	5/176 (3%)

‡: One child in the standard treatment group died (of a retroperitoneal haemorrhage that was not attributable to the treatment, according to the treating physicians).

Follow-up study to DIVERSITY [5]

This is a phase-3, single-arm safety study with patients from the DIVERSITY trial, plus new patients with VTE who have already been treated with standard therapy for at least 3 months. All these children (n=203) were treated with dabigatran (median treatment duration 36.3 weeks; range 0-57 weeks).
A total of 2 out of 203 children (1.0%) had recurrent VTE during treatment and 3 out of 203 (1.5%) had major bleeding, including 2 cases (1.0%) of clinically relevant (but non-major) bleeding and 37 cases (18.2%) of minor bleeding. No deaths were reported during treatment.
Post-thrombotic syndrome during treatment was reported in 2 out of 162 children (1.2%); the recurrent VTE was deep vein thrombosis and central line thrombosis.

EINSTEIN junior study for rivaroxaban [6]
This study has already been described in our evaluation report for rivaroxaban.[7] The outcomes of that evaluation are given below.

Symptomatic VTE recurrences 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 deterioration 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.
With the help of repeated imaging, it was shown that the thrombus had dissolved in 38.2% (128 patients) in the rivaroxaban arm and 26.1% (43 patients) in the control arm.
Severe (major) haemorrhages and non-severe clinically relevant bleeding occurred in 10 children (3%) in the rivaroxaban group and in 3 children (2%) in the control arm.

Summary of the results:

	Control arm (heparin or VKA)	Rivaroxaban	
Symptomatic recurrent VTE	5/165 (3.0%)	4/335 (1.2%)	HR 0.40; 95% CI: 0.11 to 1.41
2nd outcome measure (composite end point)	6/165 (3.6%)	5/335 (1.5%)	
Thrombus resolution	43/165 (26.1%)	128/335 (38.2%)	
Bleeding	3/162 (2%)	10/329 (3%)	HR 1.58; 95% CI: 0.51-6.27

Discussion
The patient population for this review of dabigatran consists of children with venous thromboembolism. The guideline advises treating venous thrombosis in children with parenteral anticoagulation (heparin) followed by low molecular weight heparin (LMWH) or vitamin K antagonists (VKA). A DOAC can be used instead of the standard treatment with LMWH or a VKA.

Based on the DIVERSITY study comparing dabigatran directly against the standard treatment, the conclusion was that the intervention arm was not inferior (to a 20% margin) to the control arm in terms of the primary outcome measure (efficacy). The Mantel-Haenszel weighted difference was –0.04; 90%CI: –0.14 to 0.07; p<0.0001. The planned test for superiority shows that superiority could not be established (p=0.27). The adverse effects also paint a similar picture in both research arms.

In the evaluation of rivaroxaban, we concluded that rivaroxaban has added therapeutic value in the treatment of VTE in children compared to the standard treatment (low molecular weight heparin and vitamin K antagonists).[7]
Based on the design of the EINSTEIN study, no statement can be made about non-inferiority or superiority with respect to the control treatment. The results from the rivaroxaban arm of the EINSTEIN junior study seem comparable to the results with adults. Given that the current standard treatment can be difficult in children in terms of administration and monitoring, the availability of an orally administered form that is easier to dose and needs less monitoring offers added value for paediatric patients.

However, the advantage of the oral form, which is easier to administer and requires less monitoring, does not apply in the case of dabigatran. Rivaroxaban, including the pharmaceutical form with 1 mg/ml granules for oral suspension, is licensed for full-term neonates, infants and toddlers, children and adolescents. Dabigatran capsules, though, are unsuitable for children aged under 8. The claim made by the applicant (that "dabigatran is therapeutically comparable to rivaroxaban in the treatment of VTE in children") has not been proved.

Based on the above, we have concluded that dabigatran as treatment of VTE in children aged eight and older has a therapeutic value comparable to the standard treatment (low molecular weight heparin or vitamin K antagonists).

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[1] European Medicines Agency, Amsterdam. 2021. Pradaxa. Summary of product characteristics. Consulted in February 2022 via https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_nl.pdf.
[2] NVK guideline. Diagnosis and treatment of venous thromboembolic complications in neonates and children up to 18 years of age. 2014. First revision, 2020. Consulted in February 2022 via https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=123797504&tagtitles=Algemene%252bKindergeneeskunde%2CCardiologie%2CHematologie.
[3] European Medicines Agency, Amsterdam. 2021. Pradaxa-H-C-829-X0122-G: EPAR – Assessment Report – Extension. Consulted in February 2022 via https://www.ema.europa.eu/en/documents/variation-report/pradaxa-h-c-829-x-0122-g-epar-assessment-report-extension_en.pdf.
[4] Halton J, Brandão LR, Luciani M, et al. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. *Lancet Haematol*. 2021;8(1):e22-e33. doi:10.1016/S2352-3026(20)30368-9.
[5] Brandão LR, Albisetti M, Halton J, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children [published correction appears in Blood. 2020 May 7;135(19):1720]. Blood. 2020;135(7):491-504. doi:10.1182/blood.2019000998.
[6] Male C, Lensing AWA, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol. 2020;7(1):e18-e27.

doi:10.1016/S2352-3026(19)30219-4.

[7] National Health Care Institute, Diemen. 17 March 2021. GVS advisory report on rivaroxaban (Xarelto) extension – further conditions. Available at: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/03/17/gvs-advies-rivaroxaban-xarelto-bij-de-preventie-en-behandeling-van-vte-bij-kinderen.

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