Important Risk Minimisation Information for Healthcare Professionals

Pradaxa® (dabigatran etexilate) PRESCRIBER GUIDE for paediatric use

This guide provides recommendations for the use of PRADAXA® in the paediatric population in order to minimise the risk of bleeding

- Indication
- Contraindications
- Dosing
- Special patient populations potentially at high risk of bleeding
- Perioperative management
- Coagulation tests and their interpretation
- Overdose
- Management of bleeding complications
- PRADAXA® Patient Alert Card and counselling
- Special guidance for the use of the PRADAXA® oral solution
- References

This prescriber guide does not substitute the PRADAXA® Summary of Product Characteristics (SmPC)[1] which may be accessed on the European Medicines Agency web site: http://www.ema.europa.eu/

The coated granules and oral solution formulations of PRADAXA® are not yet available for use

This Educational Material is part of the conditions of the Marketing Authorisation Medicines Authority approval: March 2021

INDICATIONS

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age (paed. VTE).

CONTRAINDICATIONS

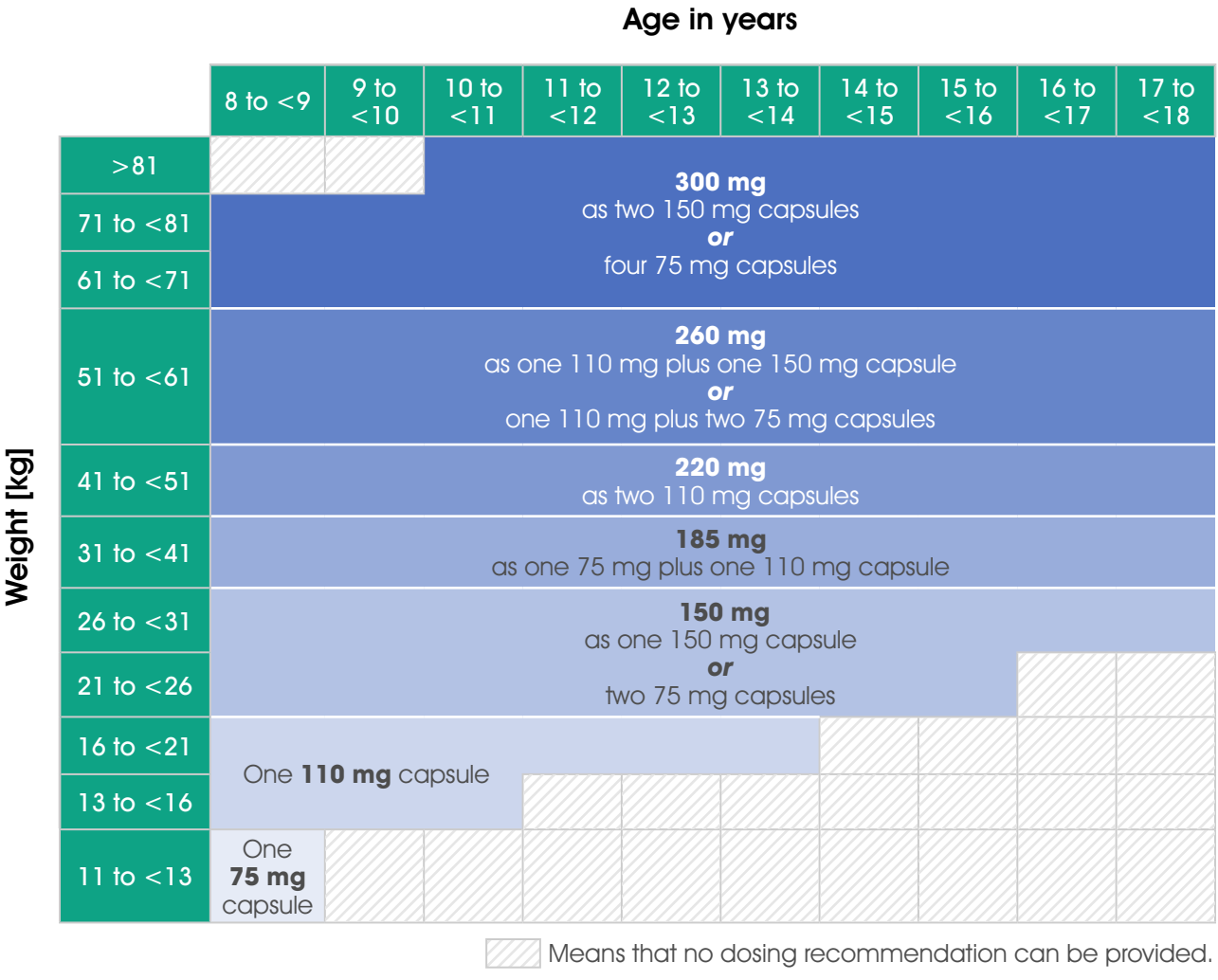
- Hypersensitivity to the active substance or to any of the excipients
- eGFR <50 mL/min/1.73m^2
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include:
  - current or recent gastrointestinal ulceration
  - presence of malignant neoplasms at high risk of bleeding
  - recent brain or spinal injury
  - recent brain, spinal or ophthalmic surgery
  - recent intracranial haemorrhage
  - known or suspected oesophageal varices
  - arteriovenous malformations
  - vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g.
  - unfractionated heparin (UFH)
  - low molecular weight heparins (enoxaparin, dalteparin etc.)
  - heparin derivatives (fondaparinux etc.)
  - oral anticoagulants (warfarin, rivaroxaban, apixaban etc.)

  except under specific circumstances. These are switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir
- Prosthetic heart valves requiring anticoagulant treatment

DOSING[1]

PRADAXA® 75 mg, 110 mg, 150 mg capsules

PRADAXA® capsules can be used in children aged 8 years or older who are able to swallow the capsules whole according to the following dosing algorithm. The dosing algorithm provides the single doses which are to be administered twice daily.



PRADAXA® 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg coated granules

PRADAXA® coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food according to the following two dosing algorithms. The dosing algorithms provide the single doses which are to be administered twice daily.

Weight [kg]	Age in months										Age in years		
	0 to <1	1 to <3	3 to <4	4 to <5	5 to <6	6 to <8	8 to <9	9 to <10	10 to <11	11 to <12	1 to <1.5	1.5 to <2	2 to <2.5
21 to <26												140	180
16 to <21											110	110	140
13 to <16									80	100	100	110	140
11 to <13							70	70	80	80	80	100	100
9 to <11					50	60	60	60	60	70	70	80	80
7 to <9			40	50	50	50	50	60	60	60	60	60	70
5 to <7	20	20	40	40	40	40	50	50	50	50	50	50	
4 to <5		20	20	20	20	40	40	40					
3 to <4			20	20	20								
2.5 to <3				20									

Means that no dosing recommendation can be provided.

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

20: One 20 mg sachet
40: One 40 mg sachet
50: One 50 mg sachet
60: Two 30 mg sachets
70: One 30 mg plus one 40 mg sachet
80: Two 40 mg sachets
100: Two 50 mg sachets
110: One 110 mg sachet
140: One 30 mg plus one 110 mg sachet
180: One 30 mg plus one 150 mg sachet

Age in years

Weight [kg]	2.5 to <4	4 to <5	5 to <6	6 to <7	7 to <9	9 to <10	10 to <12
>81							330
71 to <81					330	330	330
61 to <71				330	330	330	330
51 to <61			300	300	300	300	300
41 to <51		260	260	260	260	260	260
31 to <41	190	190	190	190	190	190	190
26 to <31	180	180	180	180	180	180	180
21 to <26	180	180	180	180	180	180	180
16 to <21	140	140	140	140	140	140	140
13 to <16	140	140	140	140	140	140	140
11 to <13	110	110	110	110	110		
9 to <11	80	80	80	80			
7 to <9	70						

Means that no dosing recommendation can be provided.

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

70: One 30 mg plus one 40 mg sachet
80: Two 40 mg sachets
110: One 110 mg sachet
140: One 30 mg plus one 110 mg sachet
180: One 30 mg plus one 150 mg sachet
190: One 40 mg plus one 150 mg sachet
260: One 110 mg plus one 150 mg sachet
300: Two 150 mg sachets
330: Three 110 mg sachets

PRADAXA® oral solution

PRADAXA® oral solution should only be used in children aged less than 1 year. The maximum dose stated in the dosing algorithm for PRADAXA® oral solution must not be exceeded. The dosing algorithm below provides the single doses which are to be administered twice daily. Do not administer PRADAXA® oral solution via feeding tubes.

Age in months

Weight [kg]	<1	1 to <2	2 to <3	3 to <4	4 to <5	5 to <6	6 to <7	7 to <8	8 to <9	9 to <10	10 to <11	11 to <12
13 to <16											12 mL	12 mL
11 to <13									10 mL	10 mL	10 mL	11 mL
9 to <11						7 mL	7 mL	8 mL	8 mL	9 mL	9 mL	9 mL
7 to <9				5 mL	6 mL	6 mL	7 mL	7 mL	7 mL	7 mL	8 mL	8 mL
5 to <7	3 mL	3 mL	4 mL	4 mL	5 mL	5 mL	5 mL	5 mL	6 mL	6 mL	6 mL	7 mL
4 to <5	2 mL	3 mL	3 mL	4 mL	4 mL	4 mL	4 mL	4 mL	5 mL	5 mL		
3 to <4	2 mL	2 mL	3 mL	3 mL	3 mL	3 mL						
2.5 to <3	2 mL	2 mL	2 mL	2 mL	3 mL							

Means that no dosing recommendation can be provided.

Oral solution [mL]	2	3	4	5	6	7	8	9	10	11	12
Contains dabigatran etexilate [mg]	12.50	18.75	25.00	31.25	37.50	43.75	50.00	56.25	62.50	68.75	75.00

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.

RECOMMENDATION FOR KIDNEY FUNCTION MEASUREMENT

- Prior to the initiation of treatment with PRADAXA®, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula.
- Treatment with PRADAXA® in patients with eGFR <50 mL/min/1.73m^2 is contraindicated (see section Contraindications).
- Patients with an eGFR ≥ 50 mL/min/1.73m^2 should be treated with the dose according to the relevant algorithm (see dosing algorithms).

***Schwartz formula:**

$$\text{eGFR (Schwartz)} = \frac{(0.413 \times \text{Height in cm})}{\text{Serum Creatinine in mg/dL}}$$

Conversion from conventional unit to SI unit:

Conventional unit *mg/mL*	Conversion 88.4	Factor SI Unit *µmol/L*

SWITCHING

PRADAXA® treatment to parenteral anticoagulant

It is recommended to wait 12 hours after the last dose before switching from PRADAXA® to a parenteral anticoagulant.

Last dose of PRADAXA®

Wait 12 hours

Start injectable anticoagulant and stop PRADAXA®

Parenteral anticoagulants to PRADAXA®

The parenteral anticoagulant should be discontinued and PRADAXA® should be started 0–2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)).

Previous injectable anticoagulant

Start PRADAXA® 0–2 hours before next dose of injectable anticoagulant is due

Do not give due dose of anticoagulant

PRADAXA® treatment to Vitamin K antagonists (VKA)

Patients with an eGFR ≥ 50 mL/min/1.73m² should start VKA 3 days before discontinuing PRADAXA®.

Patients with an eGFR < 50 mL/min/1.73m² have not been studied.
A recommendation for switching to VKA cannot be provided.

Start VKA while continuing PRADAXA®

Continue for 3 days

Stop PRADAXA®
Continue VKA

Because PRADAXA® can impact International Normalized Ratio (INR), the INR will better reflect VKA's effect only after PRADAXA® has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to PRADAXA®

The VKA should be stopped. PRADAXA® can be given as soon as the INR is < 2.0.

Stop VKA

Initiate PRADAXA®
as soon as INR is < 2.0

METHOD OF ADMINISTRATION

PRADAXA® 75 mg, 110 mg, 150 mg capsules

PRADAXA® capsules are for oral use.

- The capsules can be taken with or without food. PRADAXA® should be swallowed whole with a glass of water, to facilitate delivery to the stomach
- Do not, break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding

PRADAXA® 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg coated granules

- PRADAXA® coated granules are for oral use.
- The instructions for use must be carefully followed.

PRADAXA® oral solution

- The instructions for use provided in the package leaflet must be carefully followed. PRADAXA® oral solution should be reconstituted by a healthcare professional. Caregivers may reconstitute PRADAXA® oral solution themselves if their child´s physician determines that it is appropriate.

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Patients with an increased bleeding risk (see Table 1) should be closely monitored for signs or symptoms of bleeding or anaemia, especially if risk factors are combined. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. When clinically relevant bleeding occurs, treatment should be interrupted. For further information see "Coagulation tests and their interpretation".

The efficacy and safety of the specific reversal agent (PRAXBIND®, idarucizumab) have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options.

Table 1: Risk factors which may increase the haemorrhagic risk

Factors increasing dabigatran plasma levels	• Strong P-gp† inhibitors (see section Contraindications) • Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor)
Pharmacodynamic interactions	• Acetylsalicylic acid and other platelet aggregation inhibitors such as clopidogrel • NSAIDs • SSRIs or SNRIs† • Other medicinal products which may impair haemostasis
Diseases/procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Oesophagitis, gastritis, gastroesophageal reflux • Recent biopsy, major trauma • Bacterial endocarditis

† P-gp: P-glycoprotein; SSRIs: selective serotonin re-uptake inhibitors; SNRIs: serotonin norepinephrine re-uptake inhibitors

PERIOPERATIVE MANAGEMENT

Surgery and interventions

Patients on PRADAXA® who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of PRADAXA®.

Clearance of dabigatran in patients with renal impairment may take longer. This should be considered in advance of any procedures.

<table>
<tr><td>Emergency surgery or urgent procedures</td><td>PRADAXA® should be temporarily discontinued. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are options for reversal. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease.</td></tr>
<tr><td>Subacute surgery/ interventions</td><td>PRADAXA® should be temporarily discontinued. A surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.</td></tr>
<tr><td>Elective surgery</td><td>If possible, PRADAXA® should be discontinued at least 24 hours before invasive or surgical procedures.
Discontinuation rules before invasive or surgical procedures for paediatric patients:
<table><tr><th>Renal function (eGFR in mL/min/1.73m²)</th><th>Stop dabigatran before elective surgery</th></tr><tr><td>>80</td><td>24 hours before</td></tr><tr><td>50 – 80</td><td>2 days before</td></tr><tr><td><50</td><td>These patients have not been studied (see section Contraindications).</td></tr></table></td></tr>
<tr><td>Spinal anaesthesia/ epidural anaesthesia/ lumbar puncture</td><td>The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of PRADAXA®. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.</td></tr>
</table>

COAGULATION TESTS AND THEIR INTERPRETATION

PRADAXA® treatment does not need routine clinical monitoring[3,4].

In cases of suspected overdose or in patients treated with PRADAXA® presenting in emergency departments, it may be advisable to assess the anticoagulation status.

- The INR test is unreliable in patients on PRADAXA® and false positive INR elevations have been reported. Therefore INR tests should not be performed.
- Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity.
- Dabigatran related anticoagulation can be assessed by ECT or TT. As thrombin time (TT) is very sensitive to dabigatran, in clinical trials with paediatric patients, anticoagulant activity has been evaluated with the diluted thrombin time (dTT). This is also the preferred method.

Time point of measurement: Anticoagulant parameters depend on the time when the blood sample was taken relative to the time when the previous dose was given. A blood sample taken 2 hours after PRADAXA® ingestion (~peak level) will have different (higher) results in all clotting tests compared with a blood sample taken 10–16 hours (trough level) after ingestion of the same dose.

OVERDOSE[2,3]

Excessive anticoagulation may require interruption of PRADAXA®. Since dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience in adults to demonstrate the utility of this approach in clinical studies. PRADAXA® overdose may lead to haemorrhage. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated (see section Management of bleeding complications). General supportive measures such as application of oral activated charcoal may be considered to reduce absorption of dabigatran.

MANAGEMENT OF BLEEDING COMPLICATIONS[1,2,5]

The efficacy and safety of the specific reversal agent (PRAXBIND®, idarucizumab) have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Depending on the clinical situation appropriate standard treatment, e.g., surgical haemostasis and blood volume replacement should be undertaken. Consideration may be given to the use of fresh whole blood, fresh frozen plasma and/or platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet medicinal products have been used. Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. However, clinical data are very limited.

PRADAXA® PATIENT ALERT CARD AND COUNSELLING

A Patient alert card is provided to your patient in the PRADAXA® package. The patient or the caregiver of a paediatric patient should be instructed to carry the Patient alert card at all times and present it when seeing a health care provider. The patient or the caregiver of a paediatric patient should be counselled about the need for compliance and signs of bleeding and when to seek medical attention.

SPECIAL GUIDANCE FOR THE USE OF THE PRADAXA® ORAL SOLUTION

PRADAXA® oral solution should be reconstituted by a healthcare professional. Caregivers may reconstitute PRADAXA® oral solution themselves if their child´s physician determines that it is appropriate.

In case the anticoagulant treatment has been initiated in the hospital and has to be continued after discharge the following options are possible:

- The treatment is continued with PRADAXA® oral solution
- The treatment is continued with PRADAXA® coated granules
- The treatment is continued with standard of care

Caregivers of paediatric patients administered PRADAXA® powder and solvent for oral solution should be counselled about the reconstitution and/or dosing of the oral solution depending on which of the tasks is performed by themselves.

Please report all cases of medication errors occurring with the use of PRADAXA® oral solution to the local representative of the Marketing Authorisation Holder.

For further information and questions regarding the PRADAXA® oral solution please contact the local representative of the Marketing Authorisation Holder. Contact information for each country can be found in the package leaflet[1].

REPORTING ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

ADR Reporting - adverse events should be reported via www.medicinesauthority.gov.mt/adrportal.

Adverse events should also be reported to Boehringer Ingelheim - Malta at Vivian Corporation Limited on 80073101 (Freephone).

References

1. PRADAXA® Summary of Product Characteristics. Boehringer Ingelheim. **2.** van Ryn J *et al. Thromb Haemost* 2010; 103:1116–1127. **3.** Liesenfeld K-H *et al. Br J Clin Pharmacol* 2006; 62:527–537. **4.** Stangier J *et al. Br J Clin Pharmacol* 2007; 64:292–303. **5.** *Pollack C et al. NEJM* 2015; 373: 511–20

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NP-IE-100485 V1 | March 2021