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 PRADAXA® capsules and PRADAXA® coated granules formulations are currently available for use.
The PRADAXA® oral solution formulation is not yet available for use.

This Educational Material is part of the conditions of the Marketing Authorisation Medicines Authority approval: October 2022

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]

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

PRADAXA® should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

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. The recommended dose is based on the patient's weight and age as shown in table 1. The dose should be adjusted according to weight and age as treatment progresses. For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 1: Single and total daily doses of PRADAXA® capsules in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

Weight /age combinations		Single dose in mg	Total daily dose in mg
Weight in kg	**Age in years**		
11 to <13	8 to <9	75	150
13 to <16	8 to <11	110	220
16 to <21	8 to <14	110	220
21 to <26	8 to <16	150	300
26 to <31	8 to <18	150	300
31 to <41	8 to <18	185	370
41 to <51	8 to <18	220	440
51 to <61	8 to <18	260	520
61 to <71	8 to <18	300	600
71 to <81	8 to <18	300	600
>81	10 to <18	300	600

Single doses requiring combinations of more than one capsule:

300 mg: two 150 mg capsules or four 75 mg capsules
260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
220 mg: as two 110 mg capsules
185 mg: as one 75 mg plus one 110 mg capsule
150 mg: as one 150 mg capsule or two 75 mg capsules

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. The recommended dose is based on the patient's weight and age as shown in tables 2 and 3. The dose should be adjusted according to weight and age as treatment progresses. For weight and age combinations not listed in the dosing tables no dosing recommendation can be provided.

Table 2: Single and total daily doses of PRADAXA® coated granules in milligrams (mg) for patients aged less than 12 months. The doses depend on weight in kilograms (kg) and age in <u>months</u> of the patient.

Weight /age combinations		Single dose in mg	Total daily dose in mg
Weight in kg	**Age in MONTHS**		
2.5 to <3	4 to <5	20	40
3 to <4	3 to <6	20	40
4 to <5	1 to <3	20	40
	3 to <8	30	60
	8 to <10	40	80
5 to <7	0 to <1	20	40
	1 to <5	30	60
	5 to <8	40	80
	8 to <12	50	100
7 to <9	3 to <4	40	80
	4 to <9	50	100
	9 to <12	60	120
9 to <11	5 to <6	50	100
	6 to <11	60	120
	11 to <12	70	140
11 to <13	8 to <10	70	140
	10 to <12	80	160
13 to <16	10 to <11	80	160
	11 to <12	100	200

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

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

Table 3: Single and total daily doses of PRADAXA® coated granules in milligrams (mg) for patients aged 1 year to less than 12 years. The doses depend on weight in kilograms (kg) and age in years of the patient.

Weight / age combinations		Single dose in mg	Total daily dose in mg
Weight in kg	**Age in YEARS**		
5 to <7	1 to <2	50	100
7 to <9	1 to <2	60	120
	2 to <4	70	140
9 to <11	1 to <1.5	70	140
	1.5 to <7	80	160
11 to <13	1 to <1.5	80	160
	1.5 to <2.5	100	200
	2.5 to <9	110	220
13 to <16	1 to <1.5	100	200
	1.5 to <2	110	220
	2 to <12	140	280
16 to <21	1 to <2	110	220
	2 to <12	140	280
21 to <26	1.5 to <2	140	280
	2 to <12	180	360
26 to <31	2.5 to <12	180	360
31 to <41	2.5 to <12	220	440
41 to <51	4 to <12	260	520
51 to <61	5 to <12	300	600
61 to <71	6 to <12	300	600
71 to <81	7 to <12	300	600
>81	10 to <12	300	600

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

50 mg: One 50 mg sachet
60 mg: Two 30 mg sachets
70 mg: One 30 mg plus one 40 mg sachet
80 mg: Two 40 mg sachets
100 mg: Two 50 mg sachets
110 mg: One 110 mg sachet
140 mg: One 30 mg plus one 110 mg sachet
180 mg: One 30 mg plus one 150 mg sachet
220 mg: Two 110 mg sachets
260 mg: One 110 mg plus one 150 mg sachet
300 mg: Two 150 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 recommended dose is based on the patient's weight and age as shown in table 4. The dose should be adjusted according to weight and age as treatment progresses. For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 4: Single and total daily doses of PRADAXA® oral solution in millilitres (mL) by weight in kilograms (kg) and age in months of the patient

Weight /age combinations		Single dose in mL	Total daily dose in mL
Weight in kg	**Age in months**		
2.5 to <3	<1 to <4	2	4
	4 to <5	3	6
3 to <4	<1 to <2	2	4
	2 to <6	3	6
4 to <5	<1	2	4
	1 to <3	3	6
	3 to <8	4	8
	8 to <10	5	10
5 to <7	<1 to <2	3	6
	2 to <4	4	8
	4 to <8	5	10
	8 to <11	6	12
	11 to <12	7	14
7 to <9	3 to <4	5	10
	4 to <6	6	12
	6 to <10	7	14
	10 to <12	8	16
9 to <11	5 to <7	7	14
	7 to <9	8	16
	9 to <12	9	18
11 to <13	8 to <11	10	20
	11 to <12	11	22
13 to <16	10 to <12	12	24

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 (method used for creatinine assessment to be checked with local lab).

- 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 dosing table above (see tables 1-4).

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.

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)).

PRADAXA® treatment to Vitamin K antagonists (VKA)

Patients should start VKA 3 days before discontinuing PRADAXA®.

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.

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. For further information see section "Special guidance for the use of the PRADAXA® oral solution".

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Patients with an increased bleeding risk (see Table 5) 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.

Table 5: 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; NSAIDs: non-steroidal anti-inflammatory drugs; 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.

Emergency surgery or urgent procedures	PRADAXA® should be temporarily discontinued. Haemodialysis can remove dabigatran. Discontinuation of dabigatran therapy exposes patients to the thrombotic risk of their underlying disease.
Subacute surgery/interventions	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.
Elective surgery	If possible, PRADAXA® should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery. Discontinuation rules before invasive or surgical procedures for paediatric patients:

Renal function (eGFR in mL/min/1.73m^2)	Stop dabigatran before elective surgery
>80	24 hours before
50 – 80	2 days before
<50	These patients have not been studied (see section Contraindications).

Spinal anaesthesia/ epidural anaesthesia/ lumbar puncture	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.

COAGULATION TESTS AND THEIR INTERPRETATION

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

The measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.

- The INR test is unreliable in patients on PRADAXA® and false positive INR elevations have been reported. Therefore INR tests should not be performed.

- Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability.

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).

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.

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 by reviewing the patient alert card.

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 who were prescribed to take 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.

Once the PRADAXA® oral solution is available for use, a training video will be available to allow the correct reconstitution of the oral solution. The treating physician should confirm and document that the caregiver has understood the steps required and can independently prepare and/or administer the solution. Information about the availability of a telephone helpline should be made available to the caregiver.

Detailed instructions for use are also available in the package leaflet. Caregivers should be encouraged to read the package leaflet carefully.

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.

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.

Adverse events should be reported to Boehringer Ingelheim Drug Safety on +353 1 291 3960 or by email PV_local_uk_ireland@boehringer-ingelheim.com.

Alternatively, adverse events can also be reported to the Medicines Authority via www.medicinesauthority.gov.mt/adrportal.

References

1. PRADAXA® Summary of Product Characteristics. Boehringer Ingelheim.
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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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