Dabigatran etexilate hard capsules

PRESCRIBER GUIDE

for paediatric use

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

This prescriber guide does not substitute the dabigatran etexilate Summary of Product Characteristics,[1] which may be accessed at www.medicines.org.uk/emc/

Date of preparation: February 2024 | Version 1.0 | Approved by MHRA: April 2024

CONTENTS

INDICATION

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

RECOMMENDED DAILY DOSE

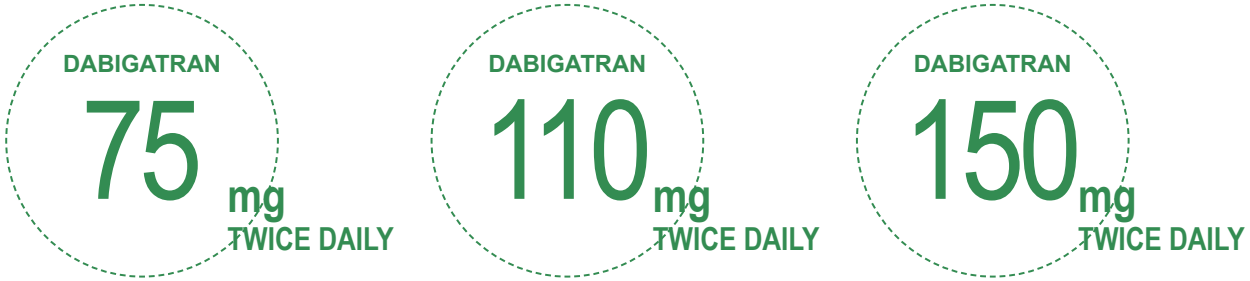


Table 1: Single and total daily doses of dabigatran etexilate capsules in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

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

When changing between the formulations (capsules, coated granules or oral solution), the prescribed dose may need to be altered. The dose stated in the SmPC of a formulation should be prescribed based on the weight and age of the child.

Dabigatran 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.

Dabigatran etexilate 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.

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

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 dabigatran, the estimated glomerular filtration rate (eGFR) should be assessed using the Schwartz formula (method used for creatinine assessment to be checked with local lab).
- Treatment with dabigatran in paediatric 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).

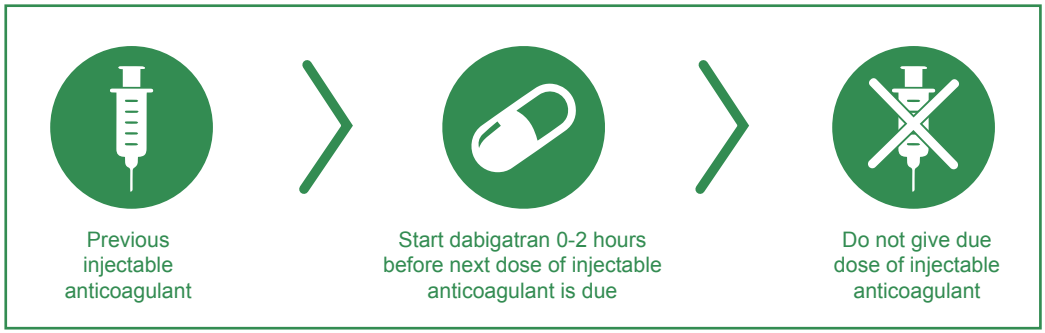
SWITCHING

Dabigatran treatment to parenteral anticoagulant

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

Parenteral anticoagulant to dabigatran

The parenteral anticoagulant should be discontinued and dabigatran 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)).



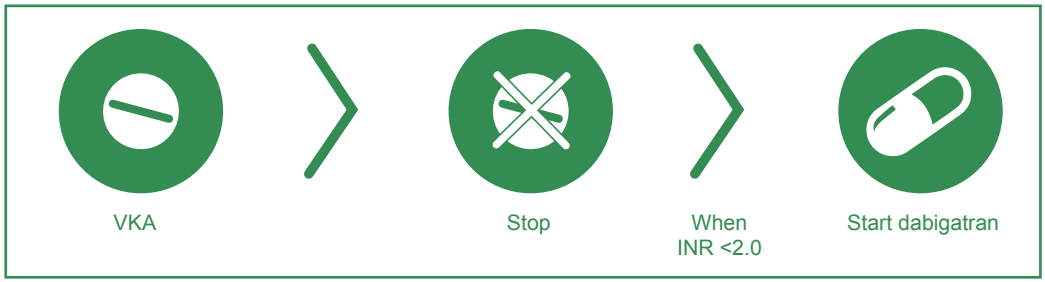
Dabigatran treatment to Vitamin K antagonists (VKA)

Patients should start VKA 3 days before discontinuing dabigatran.

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

VKA to dabigatran

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



Method of administration

Dabigatran etexilate 75 mg, 110 mg, 150 mg capsules

Dabigatran etexilate capsules are for oral use.

- The capsules can be taken with or without food. Dabigatran 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

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Patients with an increased bleeding risk (see Table 2) 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 2: 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) • The concomitant use with P-gp inhibitors has not been studied in paediatric patients but may increase the risk of bleeding
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 dabigatran who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran.

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

Dabigatran 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

Dabigatran 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, dabigatran 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 dabigatran. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

COAGULATION TESTS AND THEIR INTERPRETATION[3]

Dabigatran 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 dabigatran 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.
- Coagulation test thresholds at trough for paediatric patients that may be associated with an increased risk of bleeding are not known.

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 dabigatran 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 dabigatran. 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. Dabigatran 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.

PATIENT ALERT CARD AND COUNSELLING

A patient alert card is provided to your patient in the dabigatran 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.

References

1. Dabigatran etexilate hard capsules Summary of Product Characteristics. Glenmark Pharmaceuticals Europe Ltd.
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

REPORTING ADVERSE EVENTS AND QUALITY COMPLAINTS

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:

- the Yellow Card website **www.mhra.gov.uk/yellowcard**
- the free Yellow Card app available from the Apple App Store or Google Play Store

Alternatively you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Adverse events should also be reported to Glenmark Pharmaceuticals Europe Ltd.

If you want to report an adverse event or product quality complaint, reports can be directed via email to **Medical_information@glenmarkpharma.com** or by telephoning Glenmark Medical Information team on **0800 458 0383**.

glenmark

DABIGATRAN
PRESCRIBER GUIDE
Date of preparation: February 2024
Version 1.0 | Approved by MHRA: April 2024