Important Risk Minimisation Information for Healthcare Professionals

Dabigatran Etexilate Krka (dabigatran etexilate)

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

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

This prescriber guide does not substitute the Dabigatran Etexilate Krka Summary of Product Characteristics (SmPC)

DABIGATRAN ETEXILATE PATIENT ALERT CARD AND COUNSELLING

A Patient alert card is provided to your patient in the **Dabigatran Etexilate Krka** 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 healthcare 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.

The healthcare professionals should counsel the patient on the need to inform their healthcare professionals about all medicines the patient/ their child is currently taking and the need to inform their healthcare professionals that they/ their child are / is taking dabigatran etexilate if they/ their child need / needs to have any surgery or invasive procedure.

INDICATIONS

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

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 anticoag ulant 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 75 mg, 110 mg, 150 mg capsules

Capsules can be used in paediatric patients aged 8 years or older who are able to swallow the capsules whole.

The recommended dose of dabigatran etexilate capsules 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 continues. No dosage recommendations can be made for weight and age combinations not listed in the dosage table.

Table 1: Single and total daily doses of dabigatran etexilate in milligrams (mg) based on the patient's body weight in kilograms (kg) and age in years

Combinations of body mass and age		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 with more than one capsule:

300 mg: two 150-mg capsules or four 75-mg capsules

260 mg: one 110-mg and one 150-mg capsule or one 110-mg and two 75-mg capsules

220 mg: two 110-mg capsules

185 mg: one 75-mg and one 110-mg capsule

150 mg: one 150-mg capsule or two 75-mg capsules

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

Dabigatran etexilate 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 body weight and age as treatment continues. No dosing recommendations can be made for weight-age combinations not listed in the dosage tables.

Table 2: Single and total daily doses of dabigatran etexilate in milligrams (mg) for patients aged less than 12 months. The doses depend on the patient's body weight in kilograms (kg) and patient's age in months

Combinations of body mass and age		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 dabigatran etexilate in milligrams (mg) for patients aged 1 year to less than 12 years. Dosages depend on the patient's body weight in kilograms (kg) and the patient's age in years

Combinations of body mass and age		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

DOSING oral solution

Dabigatran etexilate oral solution should only be used in children aged less than 1 year. The maximum dose stated in the dosing algorithm for the oral solution should 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 body weight and age as treatment continues. No dosing recommendation can be made for weight and age combinations not listed in the dosage table.

Table 4: Single and total daily doses of dabigatran etexilate in milliliters (mL) according to the patient's body weight in kilograms (kg) and age in months

Combinations of body mass and age		Single dose in mg	Total daily dose in mg
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

Combinations of body mass and age		Single dose in mg	Total daily dose in mg
Weight in kg	Age in months		
5 to <7	<1 to <2	3	6
	2 to <4	4	6
	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 exilate (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 dabigatran etexilate, the estimated glomerular filtration rate (eGFR) should be assessed using the Schwartz formula (method used for creatinine assessment to be checked with local laboratory).
- Treatment with dabigatran etexilate 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 etexilate treatment to parenteral anticoagulant

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

Parenteral anticoagulants to dabigatran etexilate

The parenteral anticoagulant should be discontinued and dabigatran etexilate 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 etexilate treatment to Vitamin K antagonists (VKA)

Patients should start VKA 3 days before discontinuing dabigatran etexilate. Because dabigatran etexilate can impact International Normalised Ratio (INR), the INR will better reflect VKA's effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to dabigatran etexilate

The VKA should be stopped. Dabigatran etexilate 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. The capsules 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

Dabigatran etexilate 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg coated granules

- Coated granules are for oral use
- The instructions for use must be carefully followed

Dabigatran oral solution

- The instructions for use provided in the package leaflet must be carefully followed. Dabigatran etexilate oral solution should be reconstituted by a healthcare professional. Caregivers may reconstitute dabigatran etexilate 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 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 (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 5: Risk factors which may increase 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

* For special patient populations requiring a reduced dose, see section Dosing.
** Interaction studies have only been performed in adults.
P-gp: P-glycoprotein; NSAIDs: non-steroidal anti-inflammatory drugs; S SSRIs: selective serotonin re-uptake inhibitors; SNRIs: serotonin norepinephrine re-uptake inhibitors.

PERIOPERATIVE MANAGEMENT

Surgery and interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate. 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 etexilate should be temporarily discontinued. Haemodialysis can remove dabigatran. Discontinuation of dabigatran etexilate therapy exposes patients to the thrombotic risk of their underlying disease.

Subacute surgery/interventions

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

COAGULATION TESTS AND THEIR INTERPRETATION

Dabigatran etexilate treatment does not need routine clinical monitoring.

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

- The INR test is unreliable in patients on dabigatran etexilate 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 intertest 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 dabigatran etexilate 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

In the event of haemorrhagic complications, dabigatran etexilate treatment must be discontinued and the source of bleeding investigated (see section Management of bleeding complications). Excessive anticoagulation may require interruption of dabigatran etexilate. 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 etexilate overdose may lead to haemorrhage. General supportive measures such as application of oral activated charcoal may be considered to reduce absorption of dabigatran.

MANAGEMENT OF BLEEDING COMPLICATIONS

The efficacy and safety of the specific reversal agent (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.

SPECIAL GUIDANCE FOR THE USE OF DABIGATRAN ETEXILATE ORAL SOLUTION

Dabigatran etexilate oral solution should be reconstituted by a healthcare professional. Caregivers may reconstitute dabigatran etexilate 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 dabigatran etexilate oral solution
- The treatment is continued with dabigatran etexilate coated granules
- The treatment is continued with standard of care

Caregivers of paediatric patients who were prescribed to take dabigatran etexilate 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.

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 dabigatran etexilate oral solution to the local representative of the Marketing Authorisation Holder.

For further information and questions regarding the dabigatran etexilate 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. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie
Adverse events should also be reported to KRKA Pharmacovigilance via:
Telephone: +353 1 413 3710
Email: Info.IE@krka.biz or pharmacovigilance.IE@krka.biz

References

1. Dabigatran Etexilate Krka Summary of Product Characteristics (SmPC)

KRKA, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia