Dabigatran etexilate Accord

(dabigatran etexilate)

Important Risk Minimisation
Information for Healthcare Professionals

Prescriber Guide

The recommendations refer to the indications:

- **Stroke prevention in atrial fibrillation**
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE)**
- **Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age**
- **Primary prevention of venous thromboembolic events (VTE) following elective total hip or knee replacement surgery**

This guide provides recommendations for the use of dabigatran in order to minimise the risk of bleeding:

- Indications
- Contraindications
- Perioperative management
- Dosing
- Special patient populations potentially at higher risk of bleeding
- Coagulation tests and their interpretation
- Overdose
- Management of bleeding complications
- Dabigatran etexilate Accord Patient Alert Card and counselling

This prescriber guide does not substitute the Summary of Product Characteristics which may be accessed at **www.hpra.ie.**

Version 01: Date of HPRA Approval: October 2023

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CONTENTS

PATIENT ALERT CARD AND COUNSELLING

A Patient Alert Card is provided to your patient in the dabigatran package.

- **The patient should be instructed to carry the Patient Alert Card at all times and present it when seeing a healthcare provider.**
- **The patient should be instructed to advise the health care professional about all medicines they are currently taking.**
- **The patient should be counselled about the need for compliance and signs of bleeding and when to seek medical attention.**
- **The patient should be instructed to advise the health care professional that they are taking Dabigatran etexilate Accord if they need to have any surgery or invasive procedure.**

INDICATIONS[1,2]

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors (SPAF), such as prior stroke or transient ischaemic attack (TIA); age ≥75 years; heart failure (NYHA Class ≥II); diabetes mellitus; hypertension
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age
- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

CONTRAINDICATIONS[1-3]

- Hypersensitivity to the active substance or to any of the excipients
- eGFR <50 mL/min/1.73m^2 in paediatric patients
- Severe renal impairment (creatinine clearance [CrCL] <30 mL/min) in adult patients
- 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 or when UFH is given during catheter ablation for atrial fibrillation.
- 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.

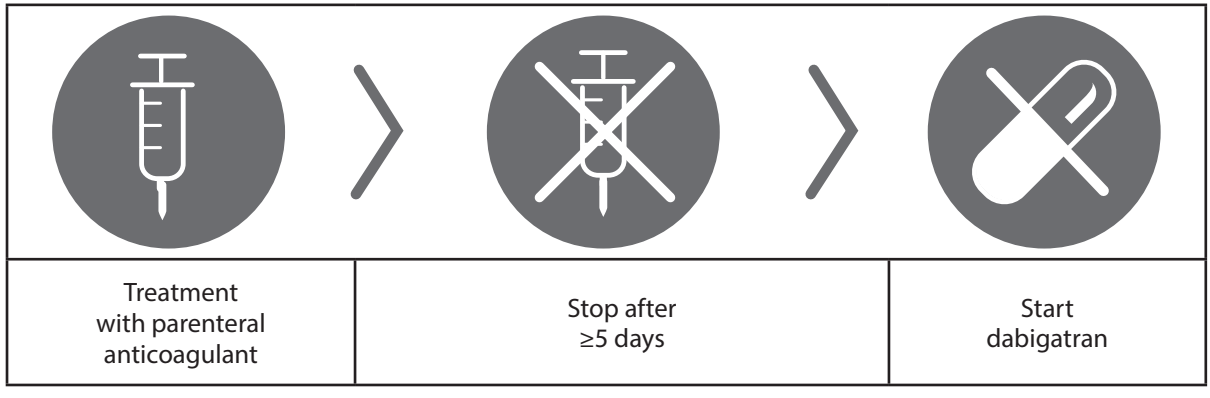
DOSING[1-3]

RECOMMENDED DAILY DOSE - Adults

DABIGATRAN 150 mg

TWICE DAILY

	Dose recommendation
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)	300 mg dabigatran taken as one 150 mg capsule twice daily
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)	300 mg dabigatran taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days



DABIGATRAN 220 mg
ONCE DAILY

	Treatment initiation on day of surgery 1–4 hours after completed surgery	Maintenance dose starting on the first day after surgery	Duration of maintenance dose
Primary prevention of VTE in adult patients following elective knee replacement surgery	Single capsule of 110 mg Dabigatran	220 mg Dabigatran once daily taken as 2 capsules of 110 mg	10 days
Primary prevention of VTE in adult patients following elective hip replacement surgery			28–35 days

Please note: If haemostasis in the post-operative phase is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery, then treatment should be initiated with 2 capsules once daily.

DOSE REDUCTION

LOWER DOSE FOR SPECIAL POPULATIONS[1-3*] - Adults

Dose reductions for indications:
- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)
- Treatment of DVT and PE, and prevention of recurrent DVT, and PE in adults (DVT/PE)

DABIGATRAN 110 mg
TWICE DAILY

Dose recommendation	
Dose reduction recommended	
Patients aged ≥80 years	Daily dose of 220 mg dabigatran taken as one 110 mg capsule twice daily
Patients who receive concomitant verapamil	
Dose reduction for consideration	
Patients between 75-80 years	Daily dose of dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding
Patients with moderate renal impairment (CrCL 30-50 mL/min)	
Patients with gastritis, oesophagitis or gastroesophageal reflux	
Other patients at increased risk of bleeding	

*Stroke prevention in atrial fibrillation; treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

DOSE REDUCTION

Dose reductions for indications:

- Primary prevention of VTE in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

DABIGATRAN 150 mg
ONCE DAILY

	Treatment initiation on day of surgery 1–4 hours after completed surgery	Maintenance dose starting on the first day after surgery	Duration of maintenance dose
Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min)	Single capsule of 75 mg Dabigatran	150 mg Dabigatran once daily taken as 2 capsules of 75 mg	10 days (knee replacement surgery) Or 28–35 days (hip replacement surgery)
Patients who receive concomitant verapamil, amiodarone, quinidine			
Patients aged 75 or above			

In patients with moderate renal impairment and concomitantly treated with verapamil, a dose reduction of Dabigatran to 75 mg once daily should be considered.

RECOMMENDED DAILY DOSE – PAEDIATRIC POPULATION

Dabigatran etexilate Accord hard 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.

<table>
<tr><th></th><th colspan="10">Age in years</th></tr>
<tr><th>Weight [kg]</th><th>8 to <9</th><th>9 to <10</th><th>10 to <11</th><th>11 to <12</th><th>12 to <13</th><th>13 to <14</th><th>14 to <15</th><th>15 to <16</th><th>16 to <17</th><th>17 to <18</th></tr>
<tr><td>>81</td><td></td><td></td><td colspan="8" rowspan="3">300 mg
as two 150 mg capsules
or
four 75 mg capsules</td></tr>
<tr><td>71 to <81</td></tr>
<tr><td>61 to <71</td></tr>
<tr><td>51 to <61</td><td colspan="9">260 mg
as one 110 mg plus one 150 mg capsule
or
one 110 mg plus two 75 mg capsules</td></tr>
<tr><td>41 to <51</td><td colspan="9">220 mg
as two 110 mg capsules</td></tr>
<tr><td>31 to <41</td><td colspan="9">185 mg
as one 75 mg plus one 110 mg capsule</td></tr>
<tr><td>26 to <31</td><td colspan="9" rowspan="2">150 mg
as one 150 mg capsule
or
two 75 mg capsules</td></tr>
<tr><td>21 to <26</td></tr>
<tr><td>16 to <21</td><td colspan="6" rowspan="2">One 110 mg capsule</td><td></td><td></td><td></td><td></td></tr>
<tr><td>13 to <16</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>11 to <13</td><td>One 75 mg capsule</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Means that no dosing recommendation can be provided

Duration of use

Indication	Duration of use
SPAF	Therapy should be continued long term.
DVT/PE	The duration of therapy should be individualised after careful assessment of treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.
VTE (in paediatric patients)	The duration of therapy should be individualised based on the benefit risk assessment.

RECOMMENDATION FOR KIDNEY FUNCTION MEASUREMENT IN ALL PATIENTS

- Renal function should be assessed by calculating the CrCL by the Cockcroft-Gault* method **prior to initiation of treatment with dabigatran** to exclude patients with severe renal impairment (i.e. CrCL <30 mL/min)
- Renal function should also be assessed when a decline in renal function is suspected **during treatment** (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)
- In elderly patients (>75 years) or patients with renal impairment, the renal function should be assessed at least once a year
- Prior to the initiation of treatment with dabigatran in paediatric patients, the estimated glomerular filtration rate (eGFR) should be assessed using the Schwartz formula (method used 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).
- Paediatric patients with an eGFR ≥ 50 mL/min/1.73m^2 should be treated with the dose according to the relevant algorithm (see dosing algorithms).

***Cockcroft-Gault formula**

For creatinine in mg/dL

$$\frac{\text{(140-age [years])} \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

For creatinine in µmol/L

$$\frac{1.23 \times \text{(140-age [years])} \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [µmol/L]}}$$

SWITCHING

Dabigatran etexilate Accord treatment to parental anticoagulant (for primary prevention of venous thromboembolic events (VTE) following elective total hip or knee replacement surgery)

It is recommended to wait 24 hours after the last dose before switching from Dabigatran etexilate Accord to a parenteral anticoagulant.

Last dose of Dabigatran etexilate Accord

Wait 24 hrs

Start injectable anticoagulant and stop Dabigatran etexilate Accord

Dabigatran etexilate Accord treatment to parenteral anticoagulant (for all other indications)

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

Last dose of Dabigatran etexilate Accord

Wait 12 hrs

Start injectable anticoagulant and stop Dabigatran etexilate Accord

Parenteral anticoagulants to Dabigatran etexilate Accord

The parenteral anticoagulant should be discontinued and Dabigatran etexilate Accord 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

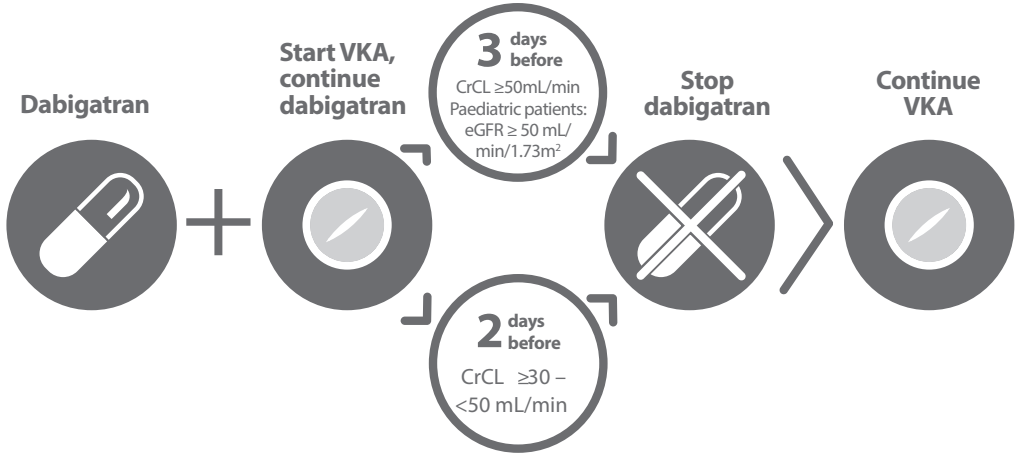
Start Dabigatran etexilate Accord 0–2 hours before next dose of injectable anticoagulant is due

Do not give due dose of injectable anticoagulant

Dabigatran etexilate Accord treatment to Vitamin K antagonists (VKA)

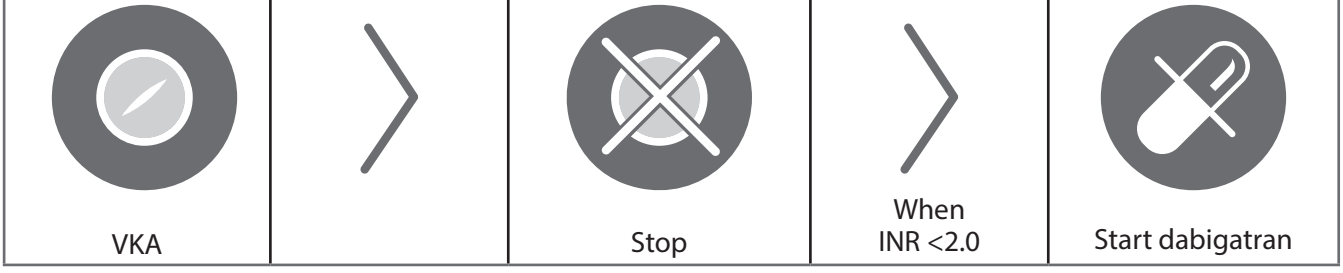
The starting time of the VKA should be adjusted based on CrCL as follows:

- CrCL ≥50 mL/min, start VKA 3 days before discontinuing dabigatran
- CrCL ≥30 – <50 mL/min, start VKA 2 days before discontinuing dabigatran
- Paediatric patients: eGFR ≥ 50 mL/min/1.73m^2, start VKA 3 days before discontinuing dabigatran



Because dabigatran can impact International Normalised 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 etexilate Accord
The VKA should be stopped. Dabigatran can be given as soon as the INR is <2.0.



Cardioversion
Patients with non-valvular atrial fibrillation treated for prevention of stroke and systemic embolism can stay on dabigatran while being cardioverted.

Catheter ablation for atrial fibrillation
Catheter ablation can be conducted in SPAF patients on 150 mg twice daily dabigatran treatment.
Dabigatran treatment does not need to be interrupted.

There are no data available for 110 mg twice daily dabigatran treatment.

Percutaneous coronary intervention (PCI) with stenting
SPAF patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with Dabigatran in combination with antiplatelets after haemostasis is achieved.

Method of administration
Dabigatran is 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 capsules since this may increase the risk of bleeding
- Dabigatran should be stored in original packaging in order to protect from moisture.

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING[1-3]

Patients with an increased bleeding risk (see Table 1 below) 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. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (see above).

A coagulation test (see section on Coagulation tests and their interpretation) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in adult patients at high risk of bleeding, a dose of 220 mg given as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent (Idarucizumab) is available.[11] 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 1*: Risk factors which may increase patients' haemorrhagic risk

Pharmacodynamic and kinetic factors	**Age ≥75 years**
Factors increasing dabigatran plasma levels	**Major:** • Moderate renal impairment (30–50 mL/min CrCL)† in adults • 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 **Minor:** • Low body weight in adults (<50 kg)
Pharmacodynamic interactions	• Acetylsalicylic acid and other platelet aggregation inhibitors such as clopidogrel • NSAID • 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 • Esophagitis, gastritis, gastroesophageal reflux • Recent biopsy, major trauma • Bacterial endocarditis

* For special patient populations requiring a reduced dose, see section Dosing.

† CrCL: Creatinine clearance; P-gp: P-glycoprotein.

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 of bleeding.
Therefore, surgical interventions may require the temporary discontinuation of dabigatran.

Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.
Please see also section 'SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING' on page 13.

Emergency surgery or urgent procedures

Dabigatran should be temporarily discontinued. When rapid reversal of the anticoagulation effect of dabigatran is required the specific reversal agent (Idarucizumab) to dabigatran is available[11]. Haemodialysis can also remove dabigatran.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran treatment can be re-initiated 24 hours after administration of idarucizumab/haemodialysis, if the patient is clinically stable and adequate haemostasis has been achieved.

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 (for cardioversion see above).

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 2–4 days before surgery. For discontinuation rules see Tables 2 and 3.

Table 2: Discontinuation rules before invasive or surgical procedures for adults

Renal function (CrCL mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥80	~13	2 days before	24 hours before
≥50-<80	~15	2-3 days before	1-2 days before
≥30-<50	~18	4 days before	2-3 days before (>48 hours)

Table 3: Discontinuation rules before invasive or surgical procedures for paediatric patients

Renal function (eGFR in mL/min/1.73m²)	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

Procedures such as spinal anaesthesia may require complete haemostatic function. 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 anticoagulant monitoring.[5,6] In cases of suspected overdose or in patients treated with dabigatran presenting in emergency departments or prior to surgery, it may be advisable to assess the anticoagulation status. The available test methods are described as follows. For further details, please refer to the Summary of Product Characteristics.

- **International Normalised Ratio (INR)**
  The INR test is unreliable in patients on dabigatran and should not be performed.

- **Activated Partial Thromboplastin Time (aPTT)**
  The aPTT test provides an approximate indication of the anticoagulation status but is not suitable for precise quantification of anticoagulant effect.

- **Dilute Thrombin Time (dTT), Thrombin Time (TT), Ecarin Clotting Time (ECT)**
  There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect.[1-4] For a quantitative measurement of dabigatran plasma concentrations, several dabigatran calibrated assays based on dTT have been developed.[7–10] A diluted TT measure[1-3] (dTT) of **>67 ng/mL (for indications of VTE in adults) and >200 ng/mL (for indications of SPAF or DVT/PE in adults) dabigatran plasma concentration prior to the next medicinal product intake** may be associated with a higher risk of bleeding. A normal dTT measurement indicates no clinical relevant anticoagulant effect of dabigatran. TT and ECT may provide useful information, but results should be interpreted with caution due to inter-test variability.

Tables 4 and 5 Coagulation test thresholds at trough (i.e. prior to the next medicinal product intake) that may be associated with an increased risk of bleeding in adults.

Please note: in the first 2–3 days after surgery, there may be greater test variability therefore results should be interpreted with caution

Test (trough value) (for indications of VTE in adults)	
dTT [ng/mL]	>67
ECT [x-fold upper limit of normal]	No data*
aPTT [x-fold upper limit of normal]	>1.3
INR	Should not be performed

* The ECT was not measured in patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg Dabigatran etexilate Accord once daily.

Test (trough value) (for indications of SPAF or DVT/PE in adults)	
dTT [ng/mL]	>200
ECT [x-fold upper limit of normal]	>3
aPTT [x-fold upper limit of normal]	>2
INR	Should not be performed

Time point: 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[1-4]

Excessive anticoagulation may require interruption of Dabigatran etexilate Accord. In cases where overdose is suspected, coagulation tests may help to assess the bleeding risk. 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 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). General supportive measures such as application of oral activated charcoal may be considered to reduce absorption of dabigatran.

MANAGEMENT OF BLEEDING COMPLICATIONS[1-4, 11]

For situations when rapid reversal of the anticoagulant effect of dabigatran is required (life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures) the specific reversal agent (Idarucizumab) is available. The efficacy and safety of the specific reversal agent (Idarucizumab) have not been established in paediatric patients. Haemodialysis can also 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.

References

1. Dabigatran etexilate Accord 75mg hard capsules Summary of Product Characteristics.
2. Dabigatran etexilate Accord 110mg hard capsules Summary of Product Characteristics.
3. Dabigatran etexilate Accord 150mg hard capsules Summary of Product Characteristics.
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5. Liesenfeld K-H et al. Br J Clin Pharmacol 2006; 62:527–537.
6. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303.
7. Hemoclot® thrombin inhibitor assay (Hyphen BioMed, Neuville-sur Oise, France). www.clottingtesting.com
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9. Technoclot® DTI Dabigatran assay (Technoclone GmbH, Vienna, Austria). www.technoclone.com
10. INNOVANCE® DTI Assay (Siemens Healthineers GmbH, Erlangen, Germany). https://www.healthcare.siemens.com/hemostasis
11. Pollack C et al. NEJM 2015; 373:511–20.

Reporting of adverse events

Reporting adverse reactions
Reporting suspected adverse events or 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 www.hpra.ie
Healthcare professionals can also report any suspected adverse reactions to Accord Healthcare by calling 0044 1271 385 257 or by emailing: medinfo@accord-healthcare.com

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