Important Risk Minimisation Information for Healthcare Professionals

Dabigatran Etexilate (Dabigatran Etexilate)

PRESCRIBER GUIDE

The recommendations only refer to the indications:

- **Stroke prevention in atrial fibrillation (SPAF)**
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE)**

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 Patient Alert Card and counselling

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

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CONTENTS

DABIGATRAN ETEXILATE PATIENT ALERT CARD AND COUNSELLING

A Patient Alert Card is provided to your patient in the Dabigatran Etexilate 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 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 about all medicines they are currently taking
- The patient should be instructed to advise the health care professional that they are taking Dabigatran Etexilate if they need to have any surgery or invasive procedure.

INDICATIONS [1-3]

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors (SPAF), such as prior stroke or transient ischemic 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 (DVT/PE)

CONTRAINDICATIONS [1-3]

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance [CrCL] <30 mL/min)
- 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[1]
150 mg twice daily

Table 1

	Dose recommendation
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)	300 mg Dabigatran Etexilate 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 Etexilate taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days

DOSE REDUCTION
LOWER DOSE FOR SPECIAL POPULATIONS*[2]
110 mg twice daily

Table 2

Dose reduction recommended	Dose recommendation
Patients aged ≥80 years	Daily dose of 220 mg Dabigatran Etexilate 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 Etexilate 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.

Duration of use

Table 3

Indication	Duration of use
SPAF	Therapy should be continued long term
DVT/PE	The duration of therapy should be individualised after careful assessment of the 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

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 Etexilate 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.

***Cockcroft-Gault formula**

For creatinine in mg/dL

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

For creatinine in µmol/L

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

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)

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 Etexilate
- CrCL ≥30– <50 mL/min, start VKA 2 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.

Cardioversion

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

Catheter ablation for atrial fibrillation

Catheter ablation can be conducted in SPAF patients on 150 mg twice daily Dabigatran Etexilate treatment. Dabigatran Etexilate treatment does not need to be interrupted. There are no data available for 110 mg twice daily Dabigatran Etexilate 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 Etexilate in combination with antiplatelets after haemostasis is achieved.

Method of administration

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 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 4) 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 Etexilate exposure. When excessive Dabigatran Etexilate exposure is identified in patients at high risk of bleed, 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]

Table 4: 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) • Strong P-gp inhibitor comedication (see section Contraindications) • Mild to moderate P-gp inhibitor comedication (e.g. amiodarone, verapamil, quinidine and ticagrelor) **Minor:** • Low body weight (<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 • Oesophagitis, 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 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 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.

Emergency surgery or urgent procedures

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

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 (for cardioversion see above).

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. For discontinuation rules see Table 5.

Table 5: Discontinuation rules before invasive or surgical procedures

Renal function (CrCL mL/min)	Estimated half-life (hours)	Stop Dabigatran Etexilate 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)

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 [4]

Dabigatran Etexilate treatment does not need routine clinical monitoring.[5,6] In cases of suspected overdose or in patients treated with Dabigatran Etexilate 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 Etexilate 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 (dTT)[1-3] of **>200 ng/mL dabigatran plasma concentration prior to the next medicinal product intake** may be associated with a higher risk of bleeding.[1-3] A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. TT and ECT may provide useful information, but results should be interpreted with caution due to inter-test variability.

Table 6: Coagulation test thresholds at trough (i.e. prior to the next medicinal product intake) that may be associated with an increased risk of bleeding. Please note: in the first 2–3 days after surgery there may be greater test variability therefore results should be interpreted with caution.[4-5]

Test (trough value)	
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]

In the event of haemorrhagic complications, Dabigatran Etexilate treatment must be discontinued and the source of bleeding investigated (see section Management of bleeding complications). In cases where overdose is suspected, coagulation tests may help to assess the bleeding risk. 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 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 Etexilate.

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) a specific reversal agent (idarucizumab) is available. 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.

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 at www.hpra.ie.
Adverse events may also be reported to Clonmel Healthcare Ltd. via medicalinformation@clonmel-health.ie or 052 6177777

REFERENCES

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