Important Risk Minimisation Information for Healthcare Professionals

Dabigatran Etexilate Krka (dabigatran etexilate)

PRESCRIBER GUIDE

for primary prevention of venous thromboembolic events (VTE) following elective total hip or knee replacement surgery

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

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

DABIGATRAN PATIENT ALERT CARD AND COUNSELLING

A Patient alert card is provided to your patient in the **Dabigatran Etexilate Krka** 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 healthcare professionals should counsel the patient on the need to inform their healthcare professionals about all medicines the patient is currently taking and the need to inform their healthcare professionals that they are taking dabigatran etexilate if they need to have any surgery or invasive procedure.

INDICATION

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery.

CONTRAINDICATIONS

- 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 or 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

RECOMMENDED DAILY DOSE

220 mg once daily taken as 2 capsules of 110 mg

Table 1	**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 following elective knee replacement surgery	Single capsule of 110 mg dabigatran etexilate	220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg	10 days
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

150 mg once daily taken as 2 capsules of 75 mg once daily

Table 2	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 etexilate	150 mg dabigatran etexilate once daily taken as 2 capsules of 75 mg	10 days (knee replacee ment 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 etexilate to 75 mg once daily should be considered.

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 24 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 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)).

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

Patients with an increased bleeding risk (see Table 3) 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. 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 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.

Table 3: Risk factors which may increase 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 co-medication (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.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran etexilate treatment can be re-initiated 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.

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 4.

Table 4: 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

Dabigatran etexilate treatment does not need routine clinical monitoring. 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. For a quantitative measurement of dabigatran plasma concentrations, several dabigatran calibrated assays based on dTT have been developed. A diluted TT measure (dTT) of **>67 ng/mL 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 the tests are not standardised.

Table 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. 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)	
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 once daily.

Time point: Anticoagulant parameters depend on the time when the blood sample was taken as well as when the last 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 20–28 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). 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.

MANAGEMENT OF BLEEDING COMPLICATIONS

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.

The recommendations given in this prescriber guide only refer to the use of dabigatran etexilate in primary prevention of VTE following total hip or knee replacement surgery with once-daily dosing.

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)

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