ARX-Dabigatran (dabigatran etexilate) **PRESCRIBER GUIDE**

For 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:

- Indication
- Contraindications
- Perioperative management
- Dosing
- Special patient populations potentially at higher risk of bleeding
- Coagulation tests and their interpretation
- Overdose
- Management of bleeding complications
- ARX-DABIGATRAN Patient Alert Card and counselling

This prescriber guide does not substitute the ARX-Dabigatran Product Information which may be accessed via the TGA website or available from Arrotex Medical Information Department on 1800 195 055.

PATIENT ALERT CARD AND COUNSELLING

When prescribing ARX-Dabigatran, the enclosed Patient alert card should be provided to your patient, together with the GP referral letter. 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.

INDICATION

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

CONTRAINDICATIONS

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product.
- Severe renal impairment (CrCL < 30 mL/min).
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis.
- 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 anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban, etc.) except under the following specific circumstances: switching anticoagulant therapy (see Section 4.2 Dose and method of administration in the Product Information document), 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 (see Section 4.5 Interactions with other medicines and other forms of interactions in the Product Information document).
- Indwelling spinal or epidural catheter and during the first two hours after removal (see Section 4.4 Special warnings and precautions for use in the Product Information document).
- Hepatic impairment or liver disease expected to have any impact on survival.
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding.
- Gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated, e.g. by surgery.
- Conditions associated with increased risk of bleeding (see Table 1, page 8).
- Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole, dronedarone or the fixed-dose combination glecaprevir/pibrentasvir (see Section 4.4 Special warnings and precautions for use in the Product Information document).
- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.
- Prosthetic heart valve replacement.

DOSING

RECOMMENDED DAILY DOSE IS 220 mg TAKEN ORALLY AS TWO 110 mg CAPSULES 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 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
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 DAILY DOSE FOR SPECIAL POPULATIONS TAKEN AS 2 CAPSULES OF 75 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 both moderate renal impairment and concomitantly treated with verapamil, a dose reduction of dabigatran 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** 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)

*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 treatment to parenteral anticoagulant

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



Last dose of ARX-Dabigatran

Wait 24 hours

Start injectable anticoagulant and stop ARX-Dabigatran

Parenteral anticoagulants to dabigatran

The parenteral anticoagulant should be discontinued and ARX-Dabigatran 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 ARX-Dabigatran 0-2 hours before next dose of injectable anticoagulant is due

Do not give due dose of injectable anticoagulant

Switching from Vitamin K antagonists to ARX-Dabigatran

The vitamin K antagonist should be stopped. ARX-Dabigatran can be given as soon as the INR is < 2.0.

Switching from ARX-Dabigatran to Warfarin

When converting from ARX-Dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCL > 50 mL/min, start warfarin 3 days before discontinuing ARX-Dabigatran.
- For CrCL 31 – 50 mL/min, start warfarin 2 days before discontinuing ARX-Dabigatran.
- For CrCL 15 – 30 mL/min, start warfarin 1 day before discontinuing ARX-Dabigatran.
- For CrCL < 15 mL/min, no recommendations can be made.

Because dabigatran etexilate can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran etexilate has been stopped for at least 2 days.

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 capsule 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

Patients with an increased bleeding risk (see Table 1) 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 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 Praxbind® (idarucizumab) is available.

Table 1: Factors which may increase the haemorrhagic risk

Pharmacodynamic and kinetic factors	• Age ≥ 75 years
Factors increasing dabigatran plasma levels	• Moderate renal impairment (30 – 50 mL/min CrCL) • P-glycoprotein (P-gp) inhibitor co-medication (some P-gp inhibitors are contraindicated)
Pharmacodynamic interactions	• Antiplatelet agents, including acetylsalicylic acid (ASA), clopidogrel, prasugrel and ticagrelor • Non steroidal anti-inflammatory drugs (NSAIDs) • Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) • Thrombolytic agents
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastro-intestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis

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 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 should be temporarily discontinued. When rapid reversal of the anticoagulation effect of dabigatran is required the specific reversal agent Praxbind® (idarucizumab) to dabigatran is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran treatment can be re-initiated 24 hours after administration of Praxbind® (idarucizumab), 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.

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 Table 2.

Table 2: Discontinuation rules before invasive or surgical procedures

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)

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

ARX-Dabigatran does not in general require routine anticoagulation monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Coagulation testing should also be considered to assist with the management of patients in the perioperative setting, suspected overdose and emergency situations.

The available test methods are described as follows.

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.

Tests of anticoagulant activity such as Thrombin Time (TT), diluted Thrombin Time (dTT), Ecarin Clotting Time (ECT) and activated Partial Thromboplastin Time (aPTT) are available to detect excessive dabigatran activity. Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT, dTT or TT are not available, the aPTT test provides an approximation of dabigatran etexilate's anticoagulant activity.

Table 3: 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 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 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.

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 in primary prevention of VTE following total hip or knee replacement surgery with once-daily dosing.

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) the specific reversal agent Praxbind® (idarucizumab) is available.

References

1. ARX-Dabigatran Product Information



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