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

The recommendations only 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 (DVT/PE) in adults**

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
- 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.

INDICATIONS

- 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

- 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 9).
- 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

DABIGATRAN 150 mg TWICE DAILY

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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



Treatment with parenteral anticoagulant

Stop after 5 days

Start ARX-Dabigatran

DOSE REDUCTION

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

LOWER DOSE FOR SPECIAL POPULATIONS*

DABIGATRAN **110** mg TWICE DAILY

Dose reduction recommended	Dose recommendation
Patients aged≥ 75 years	Daily dose of 220 mg dabigatran taken as one 110 mg capsule twice daily
Patients with potentially higher risk of major bleeding	
Patients with moderate renal impairment (CrCL 30–50 mL/min)	
Patients who receive concomitant verapamil	Daily dose of 300 mg taken orally as a 150 mg capsule twice daily.

Limited clinical data are available for patients with multiple risk factors. In these patients, ARX-Dabigatran should only be given if the expected benefit outweighs bleeding risks.

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 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** 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 treatment to parenteral anticoagulant

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



Last dose of ARX-Dabigatran

Wait 12 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.

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 is no data available for 110 mg twice daily dabigatran treatment.

Percutaneous coronary intervention (PCI) with stenting (SPAF)

SPAF patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with ARX-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 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 overleaf) 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 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 Praxbind® (idarucizumab) is available.

Table 1: Risk factors which may increase patients' 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 (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 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 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]	>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 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 10-16 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.

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.

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. ARX-Dabigatran Product Information.

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Date of preparation: March 2024.