Pradaxa® (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 in adults (DVT/PE)**

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

- Indication
- Contraindications
- Dosing
- Special patient populations
- Coagulation tests and their interpretation
- Actions to take in overdose situations

This prescriber guide does not substitute the Pradaxa Summary of Product Characteristics[1,2], which may be accessed at www.medicines.org.uk/emc/

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 counselled about the need for compliance and signs of bleeding and when to seek medical attention.

INDICATIONS[1,2]

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, 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[1,2]

- Hypersensitivity to the active substance or to any of the excipients
- Patients with 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 of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment

ACTIVE CANCER PATIENTS WITH DVT/PE

The efficacy and safety for treatment of DVT and PE, and prevention of recurrent DVT and PE have not been established for patients with active cancer.

DOSING[1,2]

RECOMMENDED DAILY DOSE[1]

DABIGATRAN

150 mg

TWICE DAILY

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:

The recommended daily dose of dabigatran is 300 mg taken orally as one 150 mg capsule twice daily. Therapy should be continued long term.

Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (DVT/PE):

The recommended daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. 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.

LOWER DOSE FOR SPECIAL POPULATIONS*[2]

For both indications

Reduced daily dose of 220 mg (taken as one 110mg capsule twice daily) is recommended for:

- Patients aged 80 years or above
- Patients who receive dabigatran concomitantly with verapamil

Reduced daily dose of 220 mg (taken as one 110 mg capsule twice daily) should be considered for:

- Patients between 75–80 years. These patients should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. However a dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high
- Patients with gastritis, oesophagitis, or gastroesophageal reflux
- Patients with moderate renal impairment (creatinine clearance [CrCL] 30–50mL/min). The recommended dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran to 220 mg taken as one 110 mg capsule twice daily should be considered
- Other patients at increased risk of bleeding (please see overleaf)

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

Method of administration

- Dabigatran can be taken with or without food. The capsule 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

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) from treatment.

- While on treatment, renal function should be assessed when it is suspected that renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications)
- 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

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

For creatinine in μmol/L

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

This method is recommended when assessing patients' creatinine clearance prior to and during dabigatran treatment.

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING[1,2]

Patients with an increased bleeding risk (see Table 1 overleaf) should be closely monitored clinically (looking for signs of bleeding or anaemia). 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.

As with all anticoagulants, dabigatran should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined.

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 (see section "Recommendation for cases of overdose").[1,2]

Table 1* summarises 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)† • P-gp† inhibitor comedication **Minor:** • Low body weight (<50 kg)
Pharmacodynamic interactions	• Aspirin • NSAID • Clopidogrel • SSRIs or SNRIs# • Other drugs 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 the "Dosing" section.

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

SSRIs: selective serotonin re-uptake inhibitors; SNRIs: serotonin norepinephrine re-uptake inhibitors.

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 dabigatran

Wait 12 hrs

Start injectable anticoagulant and stop dabigatran

Parenteral anticoagulants to dabigatran

Discontinue the parenteral anticoagulant and start dabigatran 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

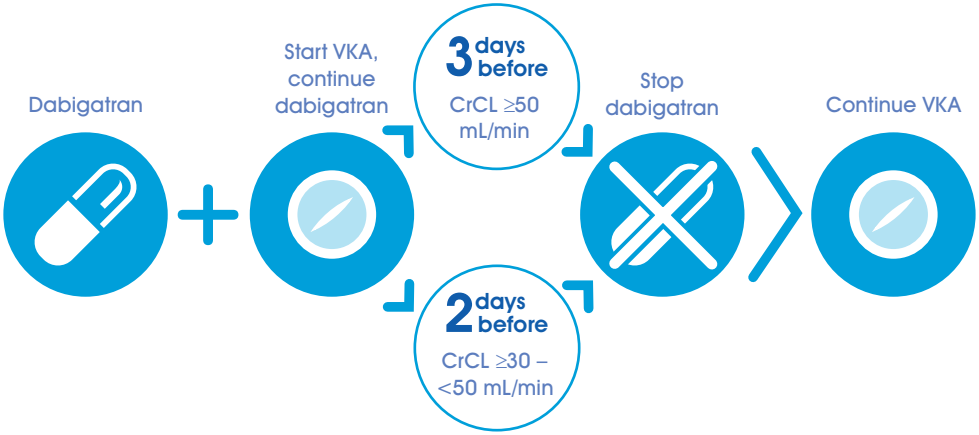
Start dabigatran 0–2 hours before next dose of injectable anticoagulant is due

Do not give due dose of injectable anticoagulant

Dabigatran treatment to Vitamin K antagonists (VKA)

Adjust the starting time of the VKA 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



Because dabigatran can increase 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

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.

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.

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. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Table 2 summarises 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[3]

Dabigatran treatment does not need routine clinical monitoring, neither for short-term nor for long-term treatment.[4,5] However, 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.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect.[1–3] Thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution.

aPTT

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution.

INR

The INR test is unreliable in patients on dabigatran and false positive INR elevations have been reported. Therefore INR tests should not be performed.

Measurement of dabigatran plasma concentrations

For a quantitative measurement of dabigatran plasma concentrations, several dabigatran assays based on diluted thrombin time have been developed.[6–8] A diluted TT measure[1,2] (dTT) of **>200 ng/mL dabigatran prior to the next drug intake** may be associated with a higher risk of bleeding.[1,2] A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran.

Table 3 shows coagulation test thresholds at trough (i.e. prior to the next drug 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.[3,4]

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.

RECOMMENDATIONS FOR CASES OF OVERDOSE[1–3]

Doses of dabigatran beyond those recommended expose the patient to an increased risk of bleeding. In cases where overdose is suspected, coagulation tests may help to determine bleeding risk. Excessive anticoagulation may require interruption of dabigatran.

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. Depending on the clinical situation appropriate standard treatment, e.g., surgical haemostasis and blood volume replacement, should be undertaken at the prescriber`s discretion. 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 drugs have been used. All symptomatic treatment has to be given according to the physician's judgment.

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.

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited.

Please note: Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests.

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleeding.

References

1. Boehringer Ingelheim. Pradaxa 150 mg hard capsules Summary of Product Characteristics. **2.** Boehringer Ingelheim. Pradaxa 110 mg hard capsules Summary of Product Characteristics. **3.** van Ryn J *et al. Thromb Haemost* 2010; 103:1116–1127. **4.** Liesenfeld K-H *et al. Br J Clin Pharmacol* 2006; 62:527–537. **5.** Stangier J *et al. Br J Clin Pharmacol* 2007; 64:292–303. **6.** Hemoclot thrombin inhibitor assay (Hyphen BioMed, Neuville-sur Oise, France). www.aniara.com **7.** HemosIL assay (Instrumentation Laboratory, Werfen Group, Barcelona, Spain) www.instrumentationlaboratory.com **8.** Technoclot DTI Dabigatran assay (Technoclone GmbH, Vienna, Austria). www.technoclone.com

Prescribing Information (SPAF and DVT/PE UK) PRADAXA (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as mesilate) **Action:** Direct thrombin inhibitor **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 ischaemic attack; 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). **Dose and Administration:** Renal function should be assessed by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 mL/min). SPAF: Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. DVT/PE: Recommended daily dose 300 mg taken as one 150 mg capsule twice daily following treatment with parenteral anticoagulant for at least 5 days. Duration of treatment should be individualised after careful assessment of the treatment benefit against risk for bleeding. Short duration of therapy (at least three 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. In case of intolerability to dabigatran, patients should be instructed to immediately consult their doctor. For patients aged 80 years or above, or those receiving concomitant verapamil, the recommended daily dose is Pradaxa 220 mg taken as 110 mg twice daily. Pradaxa and verapamil should be taken at the same time. For the following patient groups, the daily dose of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and risk of bleeding: aged 75 – 80 years; with moderate renal impairment (CrCL 30-50 mL/min); with gastritis, oesophagitis or gastroesophageal reflux; other risk of increased bleeding. Close clinical surveillance is recommended in patients with renal impairment. Use is contraindicated in patients with severe renal impairment (CrCL < 30 mL/min). In all patients assess renal function by calculating CrCL prior to initiation to exclude patients with severe renal impairment. Renal function should also be assessed when a decline in renal function is suspected. Additionally in patients > 75 years or with mild to moderate renal impairment, renal function should also be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate. Patients with an increased risk of bleeding: closely monitor clinically looking for signs of bleeding or anaemia. A coagulation test may help identify increased risk patients. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulant to Pradaxa discontinue the parenteral anticoagulant and start Pradaxa 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; if switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCL; if switching from VKA to Pradaxa stop VKA and give Pradaxa once INR <2.0. Cardioversion patients can stay on Pradaxa whilst being cardioverted. No relevant use of Pradaxa in the paediatric population in the SPAF indication. In DVT/PE indication safety and efficacy of Pradaxa in ages less than 18 years have not been established. Pradaxa can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water to facilitate delivery to the stomach. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. **Contraindications:** Hypersensitivity to any component; severe renal impairment (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 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 specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, dronedarone; prosthetic heart valves requiring anticoagulant treatment. **Warnings and Precautions:** Not recommended if liver enzymes > 2 ULN. Haemorrhagic risk: Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. For situations of life-threatening or uncontrolled bleeding, when rapid reversal of anticoagulation effect of dabigatran is required, the specific reversal agent (Praxbind, idarucizumab) is available. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCL 30 – 50 mL/min); P-glycoprotein inhibitor co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; clopidogrel; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other drugs which may impair haemostasis; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, major trauma, bacterial endocarditis, oesophagitis, gastritis or gastroesophageal reflux. Concomitant use of ticagrelor. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution medicinal products which may increase the risk of haemorrhage. The use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. Avoid concomitant administration with P-gp inducers. 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. In emergency surgery or urgent procedures, when rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to dabigatran is available. Prescribers should consult the Summary of Product Characteristics for further information relating to surgery and interventions. 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 etexilate; these patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Efficacy and safety have not been established for DVT/PE patients with active cancer. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation medicinal products; P-gp inhibitors e.g. amiodarone, quinidine, verapamil, clarithromycin, ticagrelor co-administration (close clinical surveillance); verapamil co-administration reduce Pradaxa dose to 220 mg (see above) close clinical surveillance is recommended; caution when co-administered with posaconazole; not recommended for concomitant treatment tacrolimus, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin; SSRIs or SNRIs. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.6 % in patients with atrial fibrillation treated for the prevention of stroke and SEE and 14.4 % in patients treated for DVT/PE. Bleeding occurred in 19.4% of patients in DVT/PE prevention trial RE-MEDY and in 10.5% of patients in DVT/PE prevention trial RE-SONATE. Common (≥ 1/100 to <1/10): epistaxis; gastrointestinal haemorrhage; dyspepsia; skin haemorrhage; genitourological haemorrhage, including haematuria. Additional common adverse events seen with Stroke and SEE prevention in patients with atrial fibrillation: anaemia; abdominal pain; diarrhoea; nausea. Additional common adverse event seen in patients with DVT/PE treatment and DVT/PE prevention: rectal haemorrhage. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** *110 mg* 60 capsules £51.00 150 mg 60 capsules £51.00 **Legal category** POM **MA numbers:** *110 mg* EU/1/08/442/007 (60 capsules) *150 mg* EU/1/08/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Str. 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** February 2016.

Adverse events should be reported. Reporting forms and information can be downloaded from the Medicines Authority's website at http://medicinesauthority.gov.mt/. Adverse events should also be reported to Boehringer Ingelheim - Malta at Vivian Corporation Limited on 80073101(freephone).

Boehringer Ingelheim

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