Important Risk Minimisation Information for Healthcare Professionals

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 Pradaxa® 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
- PRADAXA® Patient Alert Card and counselling

This prescriber guide does not substitute the Pradaxa Summary of Product Characteristics[1,2], which may be accessed on the European Medicines Agency web site: http://www.ema.europa.eu/

CONTENTS

PRADAXA® PATIENT ALERT CARD AND COUNSELLING

A Patient alert card is provided to your patient in the Pradaxa® 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 (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[1,2]

- 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 and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment

DOSING[1,2]

RECOMMENDED DAILY DOSE[1]

PRADAXA®
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 Pradaxa® 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 Pradaxa® taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days

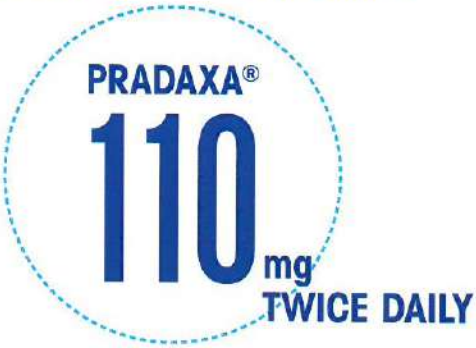
Treatment with parenteral anticoagulant

Stop after ≥5 days

Start Pradaxa®

DOSE REDUCTION

LOWER DOSE FOR SPECIAL POPULATIONS*[2]



	Dose recommendation
Dose reduction recommended	
Patients aged ≥80 years	Daily dose of 220 mg Pradaxa® 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 Pradaxa® 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	

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 Pradaxa® 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

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

For creatinine in µmol/L

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

SWITCHING

Pradaxa® treatment to parenteral anticoagulant

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

Last dose of Pradaxa®

Wait 12 hrs

Start injectable anticoagulant and stop Pradaxa®

Parenteral anticoagulants to Pradaxa®

The parenteral anticoagulant should be discontinued and Pradaxa® 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)).

Previous injectable anticoagulant

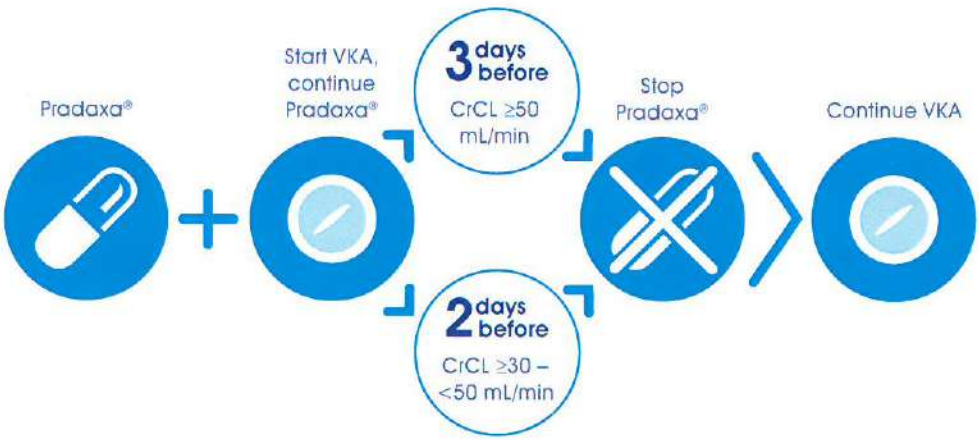
Start Pradaxa® 0–2 hours before next dose of injectable anticoagulant is due

Do not give due dose of injectable anticoagulant

Pradaxa® 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 Pradaxa®
- CrCL ≥30 – <50 mL/min, start VKA 2 days before discontinuing Pradaxa®



Because Pradaxa® can impact International Normalised Ratio (INR), the INR will better reflect VKA's effect only after Pradaxa® has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to Pradaxa®

The VKA should be stopped. Pradaxa® 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 Pradaxa® while being cardioverted.

Catheter ablation for atrial fibrillation

Catheter ablation can be conducted in SPAF patients on 150 mg twice daily Pradaxa® treatment. Pradaxa® treatment does not need to be interrupted.

There are no data available for 110 mg twice daily Pradaxa® treatment.

Percutaneous coronary intervention (PCI) with stenting

SPAF patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with Pradaxa® in combination with antiplatelets after haemostasis is achieved.

Method of administration

Pradaxa® is for oral use.

- The capsules can be taken with or without food. Pradaxa® 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

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 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.[10]

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)† • Strong P-gp† inhibitors (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 Pradaxa® who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of Pradaxa®.

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

Pradaxa® should be temporarily discontinued. When rapid reversal of the anticoagulation effect of dabigatran is required the specific reversal agent (Praxbind®, idarucizumab) to Pradaxa® is available.[10]

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa® 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

Pradaxa® 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, Pradaxa® 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 Pradaxa® 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 Pradaxa® 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 Pradaxa®. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

COAGULATION TESTS AND THEIR INTERPRETATION[3]

Pradaxa® treatment does not need routine clinical monitoring.[4,5] In cases of suspected overdose or in patients treated with Pradaxa® presenting in emergency departments or prior to surgery, it may be advisable to assess the anticoagulation status.

- **International Normalised Ratio (INR)**
  The INR test is unreliable in patients on Pradaxa® 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.[1–3] For a quantitative measurement of dabigatran plasma concentrations, several dabigatran calibrated assays based on dTT have been developed.[6–9] A diluted TT measure[1,2] (dTT) of **>200 ng/mL dabigatran plasma concentration prior to the next medicinal product intake** may be associated with a higher risk of bleeding[1,2]. 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 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.[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 Pradaxa® 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[1–3]

In cases where overdose is suspected, coagulation tests may help to assess the coagulation status. Excessive anticoagulation may require interruption of Pradaxa®. 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[1–3,10]

For situations when rapid reversal of the anticoagulant effect of Pradaxa® is required (life-threatening or uncontrolled bleeding or for emergency surgery/ urgent procedures) a 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.

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:

ADR Reporting – adverse events should be reported via www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Boehringer Ingelheim – Malta at Vivian Corporation Limited on 80073101 (Freephone)

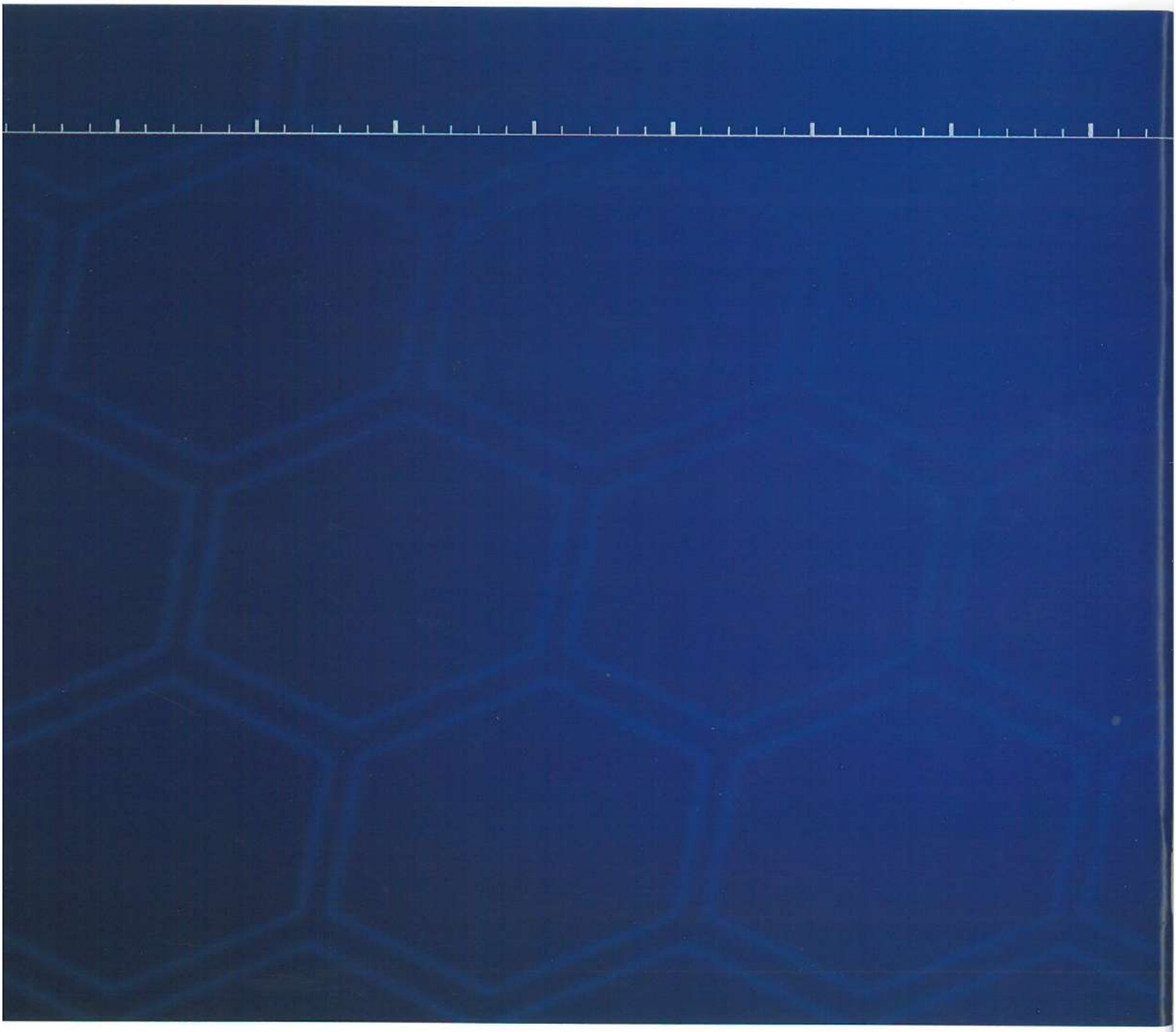
References

1. Boehringer Ingelheim. Pradaxa® 150mg hard capsules Summary of Product Characteristics. **2.** Boehringer Ingelheim. Pradaxa® 110mg 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.clottingtesting.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 **9.** INNOVANCE® DTI Assay (Siemens Healthineers GmbH, Erlangen, Germany). https://www.healthcare.siemens.com/hemostasis **10.** Pollack C *et al. NEJM* 2015; 373:511–20.

Prescribing Information (SPAF and DVT/PE Ireland)

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 (NVAF) with one or more risk factors (SPAF), such as prior stroke, or transient ischaemic 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). **Dose and Administration**: Renal function should be assessed by calculating creatinine clearance (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 gastrooesophageal 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 and especially the elderly (> 75 years) 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. 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. Catheter ablation for atrial fibrillation: Can be conducted in patients on 150 mg twice daily Pradaxa treatment - treatment does not need to be interrupted. No data available for 110 mg twice daily Pradaxa treatment. Percutaneous coronary intervention (PCI) with stenting (SPAF): Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with Pradaxa in combination with antiplatelets after haemostasis is achieved. 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 is for oral use and 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 the active substance or to any of the excipients; 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. 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-glycoprotein (P-gp) inhibitors: 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 if 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) and other platelet aggregation inhibitors such as clopidogrel; NSAID; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other medicinal products 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 gastrooesophageal reflux. The measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. When severe bleeding occurs, discontinue treatment, investigate the source of the bleeding and use of the specific reversal agent Praxbind (idarucizumab) may be considered. 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 upper limit of normal (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 (in DVT/PE patients with active cancer. **Interactions**: P-gp inhibitors - close clinical surveillance and dose reductions may be required (see above); contraindicated – ketoconazole, dronedarone, itraconazole, cyclosporine; not recommended – tacrolimus; use with caution – verapamil, amiodarone, quinidine, clarithromycin, ticagrelor, posaconazole. P-gp inducers e.g. rifampicin, St John's wort, carbamazepine or phenytoin - use should be avoided. Protease inhibitors e.g. ritonavir and its combinations with other protease inhibitors – use not recommended. Anticoagulants and antiplatelet aggregation medicinal products: SSRIs or SNRIs: 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. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. **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 systemic embolism (SED) 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. Adverse reactions identified from the study in prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation and the studies in DVT/PE treatment and in DVT/PE prevention are listed with frequency using the following convention: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), not known (cannot be estimated from the available data). *Stroke and SEE*: Common: anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; skin haemorrhage, genitourological haemorrhage, including haematuria. Uncommon: haemoglobin decreased; thrombocytopenia; drug hypersensitivity; rash; pruritus; intracranial haemorrhage; haematoma; haemorrhage; haemoptysis; rectal haemorrhage; haemorrhoidal haemorrhage; gastrointestinal ulcer; gastrooesophagitis; gastrooesophageal reflux disease; vomiting; dysphagia; hepatic function abnormal/ liver function test abnormal; alanine aminotransferase increased; aspartate aminotransferase increased. Rare: haematocrit decreased; anaphylactic reaction; angioedema; urticaria; hepatic enzyme increased; hyperbilirubinaemia; haemarthrosis; injection site haemorrhage; catheter site haemorrhage; traumatic haemorrhage; incision site haemorrhage. Not known: bronchospasm. *DVT/PE*: Common: epistaxis; gastrointestinal haemorrhage; dyspepsia; rectal haemorrhage; skin haemorrhage; genitourological haemorrhage, including haematuria. Uncommon: anaemia; drug hypersensitivity; rash; pruritus; haematoma; haemorrhage; haemoptysis; abdominal pain; diarrhoea; nausea; haemorrhoidal haemorrhage; gastrointestinal ulcer; gastrooesophagitis; gastrooesophageal reflux disease; vomiting; hepatic function abnormal/ liver function test abnormal; alanine aminotransferase increased; aspartate aminotransferase increased; hepatic enzyme increased; haemarthrosis; traumatic haemorrhage. Rare: thrombocytopenia; anaphylactic reaction; angioedema; urticaria; intracranial haemorrhage; dysphagia; injection site haemorrhage; catheter site haemorrhage; incision site haemorrhage. Not known: haemoglobin decreased; haematocrit decreased; bronchospasm; hyperbilirubinaemia. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes:** *110 mg* 60 capsules. *150 mg* 60 capsules **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. Additional information is available on request from Boehringer Ingelheim Ireland Ltd, The Crescent Building, Northwood, Santry, Dublin 9. **Prepared in** June 2018.

ADR Reporting – adverse events should be reported via www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Boehringer Ingelheim – Malta at Vivian Corporation Limited on 80073101 (Freephone)



Boehringer Ingelheim

IRE/D8G-161045(4) July 2018