Important Risk Minimisation Information for Healthcare Professionals

Pradaxa® (dabigatran etexilate) PRESCRIBER GUIDE

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

This guide provides recommendations for the use of Pradaxa®
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
- PRADAXA® Patient Alert Card and counselling

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

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.

INDICATION[1,2]

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

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 or when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment

DOSING[1,2]

RECOMMENDED DAILY DOSE

PRADAXA®
220 mg
TAKEN AS 2 CAPSULES OF 110 MG ONCE DAILY[1,2]

	Treatment initiation on day of surgery 1–4 hours after completed surgery	Maintenance dose starting on the first day after surgery	Duration of maintenance dose
Patients following elective knee replacement surgery	Single capsule of 110 mg Pradaxa®	220 mg Pradaxa® once daily taken as 2 capsules of 110 mg	10 days
Patients following elective hip replacement surgery			28–35 days

Please note: If haemostasis in the post-operative phase is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery, then treatment should be initiated with 2 capsules once daily.

DOSE REDUCTION

LOWER DOSE FOR SPECIAL POPULATIONS

PRADAXA® 150 mg TAKEN AS 2 CAPSULES OF 75 MG ONCE DAILY[1,2]

	Treatment initiation on day of surgery 1-4 hours after completed surgery	Maintenance dose starting on the first day after surgery	Duration of maintenance dose
Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min)	Single capsule of 75 mg Pradaxa®	150 mg Pradaxa® 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 moderate renal impairment and concomitantly treated with verapamil, a dose reduction of Pradaxa® 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 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)

***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 24 hours after the last dose before switching from Pradaxa® to a parenteral anticoagulant.

Last dose of Pradaxa®

Wait 24 hrs

Start injectable anticoagulant and stop Pradaxa®

Parenteral anticoagulants to Pradaxa®

The parenteral anticoagulant should be discontinued and Pradaxa® 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

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) 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.[10]

Table 1*: Risk 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† inhibitor comedication (systemic ketoconazole, cyclosporine, itraconazole and dronedarone) • 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.

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 plasma level of **>67 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]	>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 Pradaxa® 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 Pradaxa® 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[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. Pradaxa® 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.

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

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

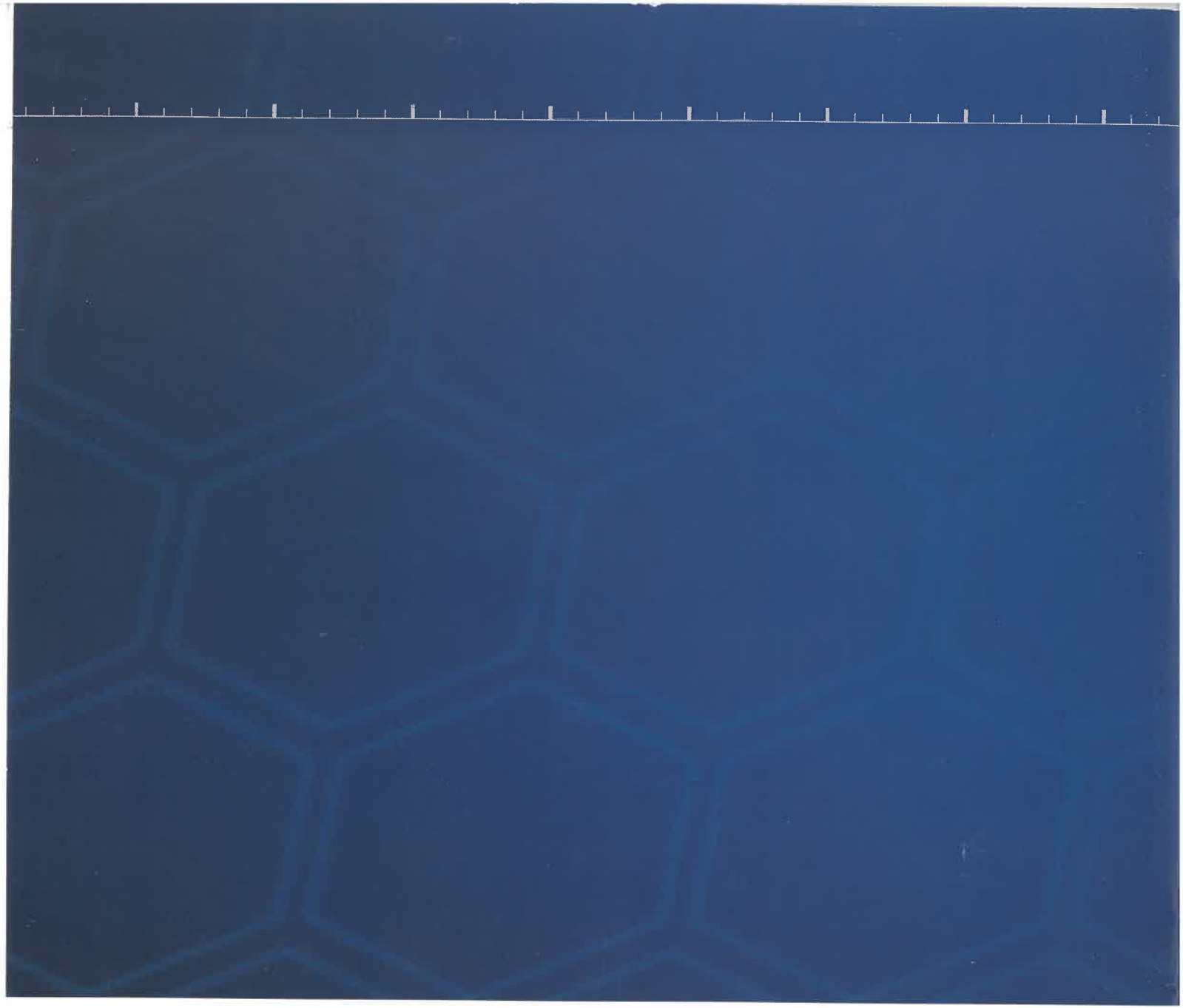
www.medicinesauthority.gov.mt/adrportal.
Adverse events should also be reported to Boehringer Ingelheim – Malta at Vivian Corporation Limited on 80073101 (Freephone)

References

1. Boehringer Ingelheim. Pradaxa® 110mg hard capsules Summary of Product Characteristics. **2.** Boehringer Ingelheim. Pradaxa® 75mg 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 (pVTEp Ireland) – PRADAXA® (dabigatran etexilate) Capsules containing 75 mg or 110 mg dabigatran etexilate (as mesilate) **Action**: Direct thrombin inhibitor **Indication**: Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery. **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). Recommended dose is 220 mg once daily orally taken as 2 capsules of 110 mg. Initiate treatment within 1-4 hours of completed surgery with a single capsule continuing with 2 capsules once daily for a total of 10 days (knee replacement surgery) or 28 – 35 days (hip replacement surgery). Delay initiation of treatment if haemostasis is not secured. If treatment is not started on the day of surgery, initiate with 2 capsules once daily. For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg: patients with moderate renal impairment (CrCL 30-50 mL/min); patients who receive concomitant verapamil, amiodarone, quinidine; patients aged 75 or above. In patients with moderate renal impairment and concomitant verapamil, consider 75 mg daily. Pradaxa is contraindicated in 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 while on treatment in certain clinical situations when it is suspected that renal function could decline or deteriorate. No dose adjustment required but close clinical surveillance in patients <. 50 kg or > 110 kg. If switching from Pradaxa to parenteral anticoagulant wait 24 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. No relevant use of Pradaxa in the paediatric population in the indication. 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 gastroesophageal 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 level 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. No data on the use of Pradaxa in patients undergoing hip fracture surgery, therefore treatment not recommended. Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. **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 14% of patients treated short-term for elective hip or knee replacement surgery; major bleeds, including wound site bleedings < 2%. Adverse reactions 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). Common: haemoglobin decreased; hepatic function abnormal/liver function test abnormal. Uncommon: anaemia; haematocrit decreased; drug hypersensitivity; haematoma; wound haemorrhage; epistaxis; gastrointestinal haemorrhage; rectal haemorrhage; haemorrhoidal haemorrhage; diarrhoea; nausea; vomiting; alanine aminotransferase increased; aspartate aminotransferase increased; hepatic enzyme increased: hyperbilirubinaemia; skin haemorrhage; haemarthrosis; genitourological haemorrhage, including haematuria; traumatic haemorrhage; post procedural haematoma; post procedural haemorrhage; post procedural discharge; wound secretion. Rare: thrombocytopenia; anaphylactic reaction; angioedema; urticaria; rash; pruritus; intracranial haemorrhage; haemorrhage; haemoptysis; gastrointestinal ulcer, including oesophageal ulcer; gastroesophagitis; gastroesophageal reflux disease; abdominal pain; dyspepsia; dysphagia; injection site haemorrhage; catheter site haemorrhage; bloody discharge; incision site haemorrhage; anaemia postoperative; wound drainage; post procedural drainage. Not known: bronchospasm. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes:** *75 mg* 10 and 60 capsules *110 mg* 10 and 60 capsules **Legal category** POM **MA numbers**: *75 mg* EU/1/08/442/001 (10 capsules); EU/1/08/442/003 (60 capsules) *110 mg* EU/1/08/442/005 (10 capsules); EU/1/08/442/007 (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** May 2019.

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)



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