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® (dabigatran etexilate) in order to minimise the risk of bleeding, including:

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

This prescriber guide does not substitute the Pradaxa® Summary of Product Characteristics (SmPC).[1,2]

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.

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 hemorrhage, 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

DOSING[1,2]

- Initiate orally within 1–4 hours of completed surgery with a dose of 110 mg (taken as one capsule of 110 mg)
- Thereafter, 220 mg (taken once daily as 2 capsules of 110 mg) for a total of 10 days (knee) or 28–35 days (hip)

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.

RECOMMENDED DAILY DOSE

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

Special patient populations with a reduced daily dose (see below):

- Patients aged 75 years or older
- Moderate renal impairment (CrCL 30–50 mL/min)
- Concomitant use of verapamil or amiodarone or quinidine

Dose recommendation for these special patient populations:

- Initiate orally within 1–4 hours of completed surgery with a dose of 75 mg (taken as one capsule of 75 mg)
- Thereafter, 150 mg (taken once daily as 2 capsules of 75 mg) for a total of 10 days (knee) or 28–35 days (hip)
- In patients with both moderate renal impairment and concomitantly treated with Pradaxa® and verapamil, a dose reduction to 75 mg daily should be considered

LOWER DOSE FOR SPECIAL POPULATIONS

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

Method of administration

- Pradaxa® 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

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) 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)

***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

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

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

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

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

As with all anticoagulants, Pradaxa® should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with Pradaxa®. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. 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 (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 • Oeophagitis, 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

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®

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 (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

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.

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. 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 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, neither for short-term nor for long-term treatment.[4,5] However, 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.

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 Pradaxa® 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 plasma level[1,2] of **>67 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]	>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.

RECOMMENDATIONS FOR CASES OF OVERDOSE[1–3]

Doses of Pradaxa® 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 Pradaxa®.

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 Pradaxa® is required (life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures) a 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 bleedings.

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2

Tel: +353 1 6764971
Fax: +353 1 6762517

Website: www.hpra.ie
E-mail: medsafety@hpra.ie

Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 1850 946100.

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.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 (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 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 75mg daily. Pradaxa is contraindicated in severe renal impairment (CrCL < 30 mL/min). Assess renal function by calculating CrCL prior to initiation to exclude patients with severe renal impairment. As renal impairment may be frequent in the elderly (> 75 years), assess renal function 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. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). 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 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. 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. **Interactions:** Anticoagulants and antiplatelet aggregation medicinal products; P-gp inhibitors co-administration (close clinical surveillance): amiodarone, quinidine, verapamil reduce Pradaxa dose to 150mg (see above); consider dose reduction to 75 mg daily in patients with both moderate renal impairment and on verapamil; close monitoring with clarithromycin and ticagrelor; 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 14% of patients treated short-term for elective hip or knee replacement surgery; major bleeds, including wound site bleedings < 2%. Common (≥ 1/100 to <1/10): haemoglobin decreased; hepatic function abnormal/liver function test abnormal. 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 2017.

Adverse events should be reported to the Health Products Regulatory Authority at www.hpra.ie or by email to medsafety@hpra.ie
Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 01 291 3960 or by email to PV_local_uk_ireland@boehringer-ingelheim.com

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