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

Pradaxa® Patient Alert Card

All patients should be provided with a Patient Alert Card and be counselled about:

- Signs or symptoms of bleeding and when to seek attention from a Healthcare Professional (HCP)
- Importance of treatment compliance
- To carry the Alert Card with them at all times
- The need to inform a HCP that they are taking Pradaxa® if they need to have any surgery or invasive procedure

~~To order copies of the patient alert card, please go to www.pradaxa.co.uk/pVTEeducationalpack~~

Indication[1,2]

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

Dosing[1,2]

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

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

- Patients aged 75 years or older.
- Moderate renal impairment (creatinine clearance (CrCL) 30-50ml/min). Treatment with Pradaxa® in patients with severe renal impairment (CrCL <30ml/min) is contraindicated.
- 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 single capsule (75mg).
- Thereafter, 150mg (taken once daily as 2 capsules of 75mg) 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 75mg daily should be considered.
- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa® in order to exclude patients with severe renal impairment (i.e., CrCL <30ml/min) from treatment. While on treatment, renal function should be assessed in certain clinical situations when it is suspected that renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications).

Method of administration

Pradaxa® can be taken with or without food. The capsule should be swallowed whole with some water. 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 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.

Table 1* (below) summarises factors which may increase the 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 (<50kg)
Pharmacodynamic interactions	• Aspirin • NSAID • Clopidogrel
Diseases/procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative GI disease • Recent GI bleeding • Recent biopsy or major trauma • Recent ICH† • Brain, spinal, or ophthalmic surgery • Bacterial endocarditis

† CrCL: Creatinine clearance; P-gp: P-glycoprotein; ICH: intracranial hemorrhage

* For special patient populations requiring a reduced dose see the "Dosing" section.

Surgery and interventions

Patients on Pradaxa® who undergo further surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of Pradaxa®.

Preoperative phase

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

Table 2 (below) summarises discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in 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)

If an acute intervention is required, Pradaxa® should be temporarily discontinued. Any surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Coagulation tests and their interpretation*[3]

Pradaxa® treatment does not need routine clinical monitoring, neither for short-term nor for long-term treatment. 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 of a patient treated with Pradaxa®. There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. The following tests may serve to assess the risk of bleeding (see Figure 1).

- **Activated partial thromboplastin time (aPTT)** test may be useful in qualitatively determining an excess of anticoagulant activity. However, aPTT is less sensitive at high plasma concentrations of dabigatran.[1-3] **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]
  - **An aPTT >45 seconds at trough (when the next dose is due)** is associated with a higher risk of bleeding.[7]

- The actual **Thrombin Time (TT)** test measure will depend on the coagulometer and the thrombin lot used for the measurement. It is therefore advisable to use the **calibrated Hemoclot® Thrombin Inhibitor assay**[5] (a diluted TT assay) with dabigatran standards to calculate the dabigatran concentration rather than to determine TT.[3]
  - A TT measure[1,2] with the **calibrated Hemoclot® thrombin inhibitor assay**[5] (Hyphen BioMed, Neuville-sur-Oise, France) of **>67 ng/mL dabigatran plasma concentration** (approximately >40 seconds) prior to the next drug intake (trough measure, i.e., 20-28 hours after the previous dose) is associated with a higher risk of bleeding.[7]
  - A normal TT measurement indicates no clinically relevant anticoagulant effect of dabigatran.
- **Ecarin Clotting Time (ECT)** provides a direct measure of the activity of direct thrombin inhibitors.[3]
  - **Approximately 2 times elevated ECT compared with normal levels prior to the next drug intake** of Pradaxa® is associated with a higher risk of bleeding.[7]
- **Prothrombin time (INR)** is not sufficiently sensitive and cannot be recommended.[3]
- **Time point:** Anticoagulant parameters depend on the time when the blood sample was taken relative to 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 (see Figure 1 which illustrates the situation after a single dose of dabigatran etexilate [Pradaxa®])

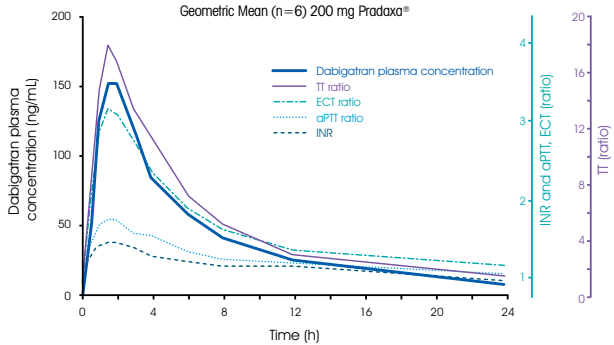

Figure 1. Example of correlation of coagulation parameters with dabigatran clearance of a 200-mg dose. Diagram taken from reference 6.

Please note: To assess the risk of bleeding, qualitative tests may be used such as aPTT, ECT or TT other than the dabigatran calibrated Hemoclot® thrombin inhibitor assay. For a quantitative measurement of dabigatran plasma concentrations only the dabigatran calibrated Hemoclot® thrombin inhibitor assay is available.[5]

* Coagulation tests are less meaningful on the day of surgery and should be interpreted with caution. While the mechanism underlying this response immediately after surgery remains unclear, perioperative effects, such as the transfusion of large volumes of fluids and/or perioperative bleeding, may contribute.[3]

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 discontinuation of Pradaxa®. There is currently no antidote to dabigatran. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies. 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. The initiation of 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 or fresh frozen plasma. **There is some experimental evidence** to support the role of agents such as activated prothrombin complex concentrates (e.g., FEIBA), recombinant Factor VIIa or concentrates of coagulation factors II, IX or X in reversing the anticoagulant activity of dabigatran.[3] **The usefulness in clinical settings has not yet been systematically demonstrated.**[3] Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.[8] All symptomatic treatment has to be given according to the physician's judgement.

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. Hemoclot® thrombin inhibitor assay (Quadratech Diagnostics Ltd). Available at www.quadratech.co.uk.
6. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303.
7. Data on file –DBG 11–05. Boehringer Ingelheim.
8. Guidelines for the use of platelet transfusions. Br J Haem 2003; 122:10-23

This prescriber guide does not substitute the Pradaxa® Summary of Product Characteristics (SmPC).

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.

Prescribing Information (pVTEp UK) – 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. In patients with moderate renal impairment (CrCL 30-50 ml/min); the elderly (age > 75 years); concomitant amiodarone, quinidine or verapamil (take at the same time as Pradaxa) the recommended dose is 150 mg once daily; moderate renal impairment and concomitant verapamil consider 75 mg 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 anticoagulants to Pradaxa then Pradaxa should be given 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. Not recommended aged < 18 years. Pradaxa should be swallowed whole with water, with or without food. 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; organic lesion at risk of bleeding; impairment of haemostasis; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, tacrolimus. **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. 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; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative GI disease, recent GI bleeding, recent biopsy or major trauma, recent ICH or brain, spinal or ophthalmic surgery, bacterial endocarditis. 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 agents 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; prescribers should consult the Summary of Product Characteristics for further information. 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. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation agents; strong 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; not recommended for concomitant treatment: posaconazole, dronedarone, 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. 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, <1/10): anaemia; haemoglobin decreased; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; hepatic function abnormal/liver function test abnormal. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** *75 mg* 10 capsules £12.60; 60 capsules £75.60 *110 mg* 10 capsules £12.60; 60 capsules £75.60 **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, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** March 2012.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

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