The recommendations given in this prescriber guide only refer to the use of Pradaxa in the indication of primary VTE prevention with once daily dosing.

This guide provides recommendations for the use of Pradaxa (dabigatran etexilate) in order to minimize the risk of bleeding.
This prescriber guide does not substitute the Pradaxa Summary of Product Characteristics (SmPC).
**INDICATION**

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.1

**CONTRAINDICATIONS**

- 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 or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal 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 (tinzaparin, 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

**DOSES1**

- Initiate orally within 1–4 hours of completed surgery as a single capsule (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 hemostasis 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 (CrCl 30–50 mL/min)
- Concomitant use of verapamil or amiodarone or quinidine

**Dose recommendation for special patient populations:**

- Initiate orally within 1–4 hours of completed surgery as a single capsule (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 moderate renal impairment and concomitantly treated with Pradaxa and verapamil, a dose reduction to 75 mg daily should be considered

**RECOMMENDED DAILY DOSE TAKEN AS 2 CAPSULES OF 110 mg ONCE DAILY**

**LOWER DOSE FOR SPECIAL POPULATIONS TAKEN AS 2 CAPSULES OF 75 mg ONCE DAILY**
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 in order to exclude patients with severe renal impairment (i.e. CrCL <30 mL/min) from treatment
- While on treatment, renal function should be assessed at least once a year or more frequently in certain clinical situations 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

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

For creatinine in μmol/L

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

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment.

**SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING**

Patients with an increased bleeding risk (see Table 1 overleaf) should be closely monitored clinically (looking for signs of bleeding or anemia). A coagulation test (see "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 hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. When clinically relevant bleeding occurs, treatment should be interrupted.
Table 1* summarizes factors which may increase the hemorrhagic risk

<table>
<thead>
<tr>
<th>Pharmacodynamic and kinetic factors</th>
<th>Age ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors increasing dabigatran plasma levels</td>
<td>Major:</td>
</tr>
<tr>
<td></td>
<td>• Moderate renal impairment (30–50 mL/min CrCl)†</td>
</tr>
<tr>
<td></td>
<td>• P-gp† inhibitor comedication (some P-gp inhibitors are contraindicated)</td>
</tr>
<tr>
<td></td>
<td>Minor:</td>
</tr>
<tr>
<td></td>
<td>• Low body weight (&lt;50 kg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacodynamic interactions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• ASA</td>
</tr>
<tr>
<td></td>
<td>• NSAID</td>
</tr>
<tr>
<td></td>
<td>• Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>• SSRIs or SNRIs†</td>
</tr>
<tr>
<td></td>
<td>• Other drugs which may impair hemostasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diseases/procedures with special hemorrhagic risks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Congenital or acquired coagulation disorders</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia or functional platelet defects</td>
</tr>
<tr>
<td></td>
<td>• Recent biopsy, major trauma</td>
</tr>
<tr>
<td></td>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>• Esophagitis, gastritis, gastroesophageal reflux</td>
</tr>
</tbody>
</table>

* 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.

![Switching Diagram]

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]).

![Switching Diagram]
Spinal anesthesia/epidural anesthesia/lumbar puncture

Procedures such as spinal anesthesia may require complete hemostatic function. The risk of spinal or epidural hematoma 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 hematoma.

Coagulation tests and their interpretation

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.

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

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.

Preoperative phase

Table 2 summarizes discontinuation rules before invasive or surgical procedures

<table>
<thead>
<tr>
<th>Renal function (CrCl mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>13</td>
<td>High risk of bleeding or major surgery</td>
</tr>
<tr>
<td>≥50 – &lt;80</td>
<td>15</td>
<td>2 days before 24 hours before</td>
</tr>
<tr>
<td>≥30 – &lt;50</td>
<td>18</td>
<td>2–3 days before 1–2 days before</td>
</tr>
<tr>
<td>(&gt;48 hours)</td>
<td></td>
<td>4 days before 2–3 days before</td>
</tr>
</tbody>
</table>

If an acute intervention is required, 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, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Spinal anesthesia/epidural anesthesia/lumbar puncture

Procedures such as spinal anesthesia may require complete hemostatic 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 hematoma.

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 (dTT) are available. A dTT measure of >67 ng/mL dabigatran plasma concentration prior to the next drug intake may be associated with a higher risk of bleeding. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran.

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.
Doses of Pradaxa beyond those recommended expose the patient to an increased risk of bleeding. In case of an overdose suspicion, coagulation tests may help to determine bleeding risk. Excessive anticoagulation may require interruption of Pradaxa. There is currently no antidote to dabigatran. In the event of hemorrhagic 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 supportive treatment, e.g. surgical hemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion.1,2

As protein binding is low, dabigatran can be dialyzed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies. Consideration may be given to the use of fresh whole blood or fresh frozen plasma. Activated prothrombin complex concentrates (e.g. FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. 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 are very limited.

**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, false prolonged measures may be detected.2,3**

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>dTT [ng/mL]</td>
<td>&gt;67</td>
<td></td>
</tr>
<tr>
<td>ECT [x-fold upper limit of normal]</td>
<td>No data*</td>
<td></td>
</tr>
<tr>
<td>aPTT [x-fold upper limit of normal]</td>
<td>&gt;1.3</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>Should not be performed</td>
<td></td>
</tr>
</tbody>
</table>

*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**

Doses of Pradaxa beyond those recommended expose the patient to an increased risk of bleeding. In case of an overdose suspicion, coagulation tests may help to determine bleeding risk. Excessive anticoagulation may require interruption of Pradaxa. There is currently no antidote to dabigatran. In the event of hemorrhagic 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 supportive treatment, e.g. surgical hemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion.1,2

Coagulation tests may become unreliable following administration of suggested reversing agents. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of 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 judgement.

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

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PRADAXA PATIENT ALERT CARD AND COUNSELING

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

References
   www.clottingtesting.com
6. HemosIL® assay (Instrumentation Laboratory, Werfen Group, Barcelona, Spain).
   www.instrumentationlaboratory.com
7. Technoclot® DTI Dabigatran assay (Technoclone GmbH, Vienna, Austria).
   www.technoclone.com/products/coagulation/control-plasma/dabigatrancont

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