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 minimize the risk of bleeding.

Updated January 2015
**Indications**

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke, transient ischemic attack (TIA); age ≥75 years; heart failure (NYHA Class ≥II); diabetes mellitus; hypertension

**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, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

**Active Cancer Patients with DVT/PE**

The efficacy and safety for treatment of DVT and PE, and prevention of recurrent DVT/PE have not been established for patients with active cancer.

This prescriber guide does not substitute the Pradaxa Summary of Product Characteristics (SmPC).
Reduced daily dose of 220 mg (taken as one 110 mg capsule twice daily) recommended:

- Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily.
- In patients who receive concomitantly Pradaxa and verapamil, dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily.

For other patients at increased risk of bleeding (see page 7–8):
- Patients between 75–80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.
- For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg given as one 110 mg capsule twice daily may be considered.
- For patients with moderate renal impairment (CrCL 30–50 mL/min), the recommended dose of Pradaxa is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of Pradaxa to 220 mg taken as one 110 mg capsule twice daily should be considered.
- Other patients at increased risk of bleeding should be considered.

PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION:

The recommended daily dose of Pradaxa is 300 mg taken orally as one 150 mg capsule twice daily. Therapy should be continued long term.

TREATMENT OF DVT AND PE, AND PREVENTION OF RECURRENT DVT AND PE IN ADULTS (DVT/PE):

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualized 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, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

TREATMENT WITH PARENTERAL ANTICOAGULANT

STOP AFTER ≥5 DAYS

START PRODAAXA

*Stroke prevention in atrial fibrillation; treatment of DVT and PE, and prevention of recurrent DVT and PE.
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).
- 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

\[
\text{CrCL} = \left(\frac{140-\text{age}}{\text{weight}}\right) \times \text{serum creatinine (mg/dL)}
\]

\[
= \left(\frac{140-\text{age}}{\text{weight}} \times 0.85 \text{ if female}\right) \times \text{serum creatinine (mg/dL)}
\]

For creatinine in μmol/L

\[
\text{CrCL} = \left(\frac{140-\text{age}}{\text{weight}}\right) \times \text{serum creatinine (μmol/L)}
\]

\[
= \left(\frac{140-\text{age}}{\text{weight}} \times 0.85 \text{ if female}\right) \times \text{serum creatinine (μmol/L)}
\]

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). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see "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 bleeding, a dose of 220 mg given as one 110 mg capsule twice daily is recommended.

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. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined.
PRADAXA PRESCRIBER GUIDE

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
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 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

---

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

<table>
<thead>
<tr>
<th>Diseases/procedures with special hemorrhagic risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital or acquired coagulation disorders</td>
</tr>
<tr>
<td>• Thrombocytopenia or functional platelet defects</td>
</tr>
<tr>
<td>• Recent biopsy, major trauma</td>
</tr>
<tr>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<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.
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>
<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</td>
</tr>
<tr>
<td>≥30 – &lt;50</td>
<td>−18</td>
<td>2–3 days before</td>
</tr>
<tr>
<td>(&gt;48 hours)</td>
<td></td>
<td>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.

### CARDIOVERSION

Patients with non-valvular atrial fibrillation treated for prevention of stroke and systemic embolism can stay on Pradaxa while being cardioverted.

### 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.
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 in emergency departments, 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.

### 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 >200 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.

### 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 in emergency departments, 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.

### 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 >200 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.

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dTT [ng/mL]</td>
<td>&gt;200</td>
</tr>
<tr>
<td>ECT [x-fold upper limit of normal]</td>
<td>&gt;3</td>
</tr>
<tr>
<td>aPTT [x-fold upper limit of normal]</td>
<td>&gt;2</td>
</tr>
<tr>
<td>INR</td>
<td>Should not be performed</td>
</tr>
</tbody>
</table>

**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**

**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.
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 specific 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 standard 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 VIII 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.

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.

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.

**RECOMMENDATIONS FOR CASES OF OVERDOSE**

**PRADAXA PATIENT ALERT CARD AND COUNSELING**

References

6. HemosIL® assay (Instrumentation Laboratory, Werfen Group, Barcelona, Spain). www.hemosil InstrumentationLaboratory.com