# PRESCRIBER GUIDE

# Dabigatran Teva®

**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 Dabigatran Teva®
in order to minimize the risk of bleeding

Teva Israel Ltd. P.O.B 3190 124 Dvora HaNevi'a St. Tel Aviv Phone: 1-800-805-005

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For full information about the drug please refer to Prescribing Information of Dabigatran Teva® (Dabigatran Etexilate).[1]

# IMPORTANT INFORMATION BEFORE TREATMENT INITIATION

» **Renal function should be assessed prior to initiation of treatment and during the treatment** (page 6)

» **Patient must be warned against uncontrolled use of non-prescription medicines, especially NSAIDs, which may impair renal function** (page 6)

» **In case of active gastrointestinal bleeding (hemorrhagic vomiting, hemoptysis, rectal bleeding), discontinue the treatment and refer the patient to the emergency room. Dabigatran Teva® may lead to bleeding that can be severe and in rare cases even cause death** (page 9)

» **Patients who receive concomitantly Dabigatran Teva® and anti-platelet drugs as Aspirin or Clopidogrel ("double therapy") or a combination of the two drugs ("triple therapy"), as a preventive treatment for coronary heart disease, should be closely monitored clinically** (pages 9-10)

## INDICATIONS

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- Treatment of DVT and PE, and prevention of recurrent DVT/PE in adults

## CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Patients with 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 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, 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 artrial 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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir
- Prosthetic heart valves requiring anticoagulant treatment

# DOSING[1]

RECOMMENDED DAILY DOSE


TWICE DAILY

| | Dose recommendation |
|---|---|
| **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation** | 300 mg Dabigatran Teva® taken as one 150 mg capsule twice daily |
| **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)** | 300 mg Dabigatran Teva® taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days |

Treatment with parenteral anticoagulant

Stop after ≥ 5 days

Start Dabigatran Teva®

# DOSE REDUCTION

LOWER DOSE FOR SPECIAL POPULATIONS*


TWICE DAILY

| | Dose recommendation |
|---|---|
| **Dose reduction recommended**<br>• **Patients aged ≥80 years**<br>• **Patients who receive concomitant verapamil** | Daily dose of 220 mg Dabigatran Teva® taken as one 110 mg capsule twice daily |
| **Dose reduction for consideration**<br>• **Patients between 75-80 years**<br>• **Patients with moderate renal impairment (CrCL 30-50 mL/min)**<br>• **Patients with gastritis, esophagitis or gastroesophageal reflux**<br>• **Other patients at increased risk of bleeding** | Daily dose of Dabigatran Teva® of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding |

* Stroke prevention in atrial fibrillation, treatment of DVT and PE, and prevention of recurrent DVT and PE

# Duration of use

| Indication | Duration of use |
|---|---|
| **SPAF** | Therapy should be continued long term |
| **DVT/PE** | 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 |

## Recommendation for kidney function measurement in all patients

- Renal function should be assessed by calculating the creatinine clearance (CrCL) by the Cockcroft-Gault* method prior to initiation of treatment with Dabigatran Teva® in order to exclude patients with severe renal impairment (i.e., CrCL< 30 mL/min). (There is a contraindication for prescribing the product for these patients.
- 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). In addition, 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:**

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

**For creatinine in µmol/L:**

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

# Switching

### Dabigatran Teva® treatment to parenteral anticoagulant

It is recommended to wait 12 hours after the last dose before switching from Dabigatran Teva® to a parenteral anticoagulant.


Last dose of Dabigatran Teva®

Wait 12 hrs

Start parenteral anticoagulant and stop Dabigatran Teva®

### Parenteral anticoagulants to Dabigatran Teva®

The parenteral anticoagulant should be discontinued and Dabigatran Teva® should be 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 parenteral anticoagulant

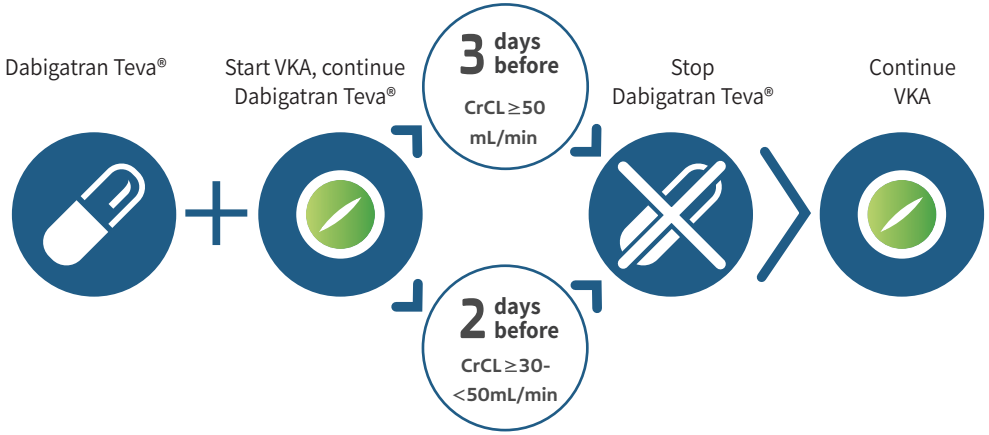
Start Dabigatran Teva® 0-2 hours before next dose of parenteral anticoagulant is due

Do not give due dose of parenteral anticoagulant

## Dabigatran Teva® treatment to Vitamin K antagonists (VKA)

The starting time of the VKA should be adjusted based on CrCL as follows:

- CrCL ≥ 50 mL/min, start VKA 3 days before discontinuing Dabigatran Teva®
- CrCL ≥ 30- < 50 mL/min, start VKA 2 days before discontinuing Dabigatran Teva®




Because Dabigatran Teva® can impact International Normalized Ratio (INR), the INR will better reflect VKA's effect only after Dabigatran Teva® has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

## VKA to Dabigatran Teva®

The VKA should be stopped. Dabigatran Teva® can be given as soon as the INR is < 2.0.

### Cardioversion

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

### Catheter ablation for atrial fibrillation

Catheter ablation can be conducted in SPAF patients on 150 mg twice daily Dabigatran Teva® treatment. Dabigatran Teva® treatment does not need to be interrupted.

There are no data available for 110 mg twice daily Dabigatran Teva® treatment.

### Percutaneous coronary intervention (PCI) with stenting

SPAF patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with Dabigatran Teva® in combination with antiplatelets after haemostasis is achieved.

### Method of administration

Dabigatran Teva® is for oral use.

- The capsules can be taken with or without food. Dabigatran Teva® 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 POPULATION POTENTIALLY AT HIGHER RISK OF BLEEDING

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 hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (see above).

A coagulation test (see section Coagulation tests and their interpretation) may help to identify patients with an increased bleeding risk caused by excessive Dabigatran Teva® exposure. When excessive Dabigatran Teva® exposure is identified in patients at high risk of bleed, a dose of 220 mg given as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

Dabigatran Teva® should be prescribed only in cases when the benefit exceeds the risk and with close clinical surveillance throughout the treatment period. 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.[9]

| Table 1: **Haemorrhagic risk factors*** | |
|---|---|
| Pharmacodynamic and kinetic factors | Age ≥75 years |
| Factors increasing dabigatran plasma levels | **Major:**<br>• Moderate renal impairment<br>• (30-50 mL/min CrCL)†<br>• Strong P-gp† inhibitors (see section Contraindications)<br>• Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor)<br>**Minor:**<br>• Low body weight (<50 kg) |
| Pharmacodynamic interactions | • Acetylsalicylic acid and other platelet aggregation inhibitors such as Clopidogrel<br>• NSAID<br>• SSRIs or SNRIs†<br>• Other medicinal products which may impair haemostasis |
| Diseases/procedures with special haemorrhagic risks | • Congenital or acquired coagulation disorders<br>• Thrombocytopenia or functional platelet defects<br>• Esophagitis, gastritis, gastroesophageal reflux<br>• Recent biopsy, major trauma<br>• 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 Dabigatran Teva® who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of Dabigatran Teva®. Clearance of Dabigatran Teva® in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

## Emergency surgery or urgent procedures

Dabigatran Teva® should be temporarily discontinued. When rapid reversal of the anticoagulation effect of Dabigatran Teva® is required the specific reversal agent (PRAXBIND®, Idarucizumab) to Dabigatran Teva® is available.[9]

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran Teva® 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

Dabigatran Teva® 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.

(For cardioversion see above).

## Elective surgery

If possible, Dabigatran Teva® 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 Dabigatran Teva® 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 Dabigatran Teva® 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 Dabigatran Teva®. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

# COAGULATION TESTS AND THEIR INTERPRETATION

Dabigatran Teva® treatment does not need routine clinical monitoring.[3,4] In cases of suspected overdose or in patients treated with Dabigatran Teva® presenting in emergency departments, it may be advisable to assess the anticoagulation status.

### International Normalised Ratio (INR)

The INR test is unreliable in patients on Dabigatran Teva® and should not be performed.

### Activated Partial Thromboplastin Time (aPTT)

The aPTT test provides an approximate indication of the anticoagulation status with Dabigatran Teva® 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 Teva® concentration and degree of anticoagulant effect.[1,2] For a quantitative measurement of Dabigatran Teva® plasma concentrations several dabigatran calibrated assays based on dTT have been developed.[5-8]

A diluted TT measure 1 (dTT) of **>200 ng/mL dabigatran plasma concentration prior to the next medicinal product intake** may be associated with a higher risk of bleeding.1 A normal dTT measurement indicates no clinical relevant anticoagulant effect of Dabigatran Teva®.

Thrombin Time (TT) and Ecarin Clotting Time (ECT) may provide useful information, but the tests are not standardized.[2]

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

| Test (trough value) | |
|---|---|
| dTT [ng/mL] | > 200 |
| ECT [x-fold upper limit of normal] | > 3 |
| aPTT [x-fold upper limit of normal] | > 2 |
| INR | Should not be performed |

**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 Dabigatran Teva® 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.

## OVERDOSE[1,2]

In case of an overdose suspicion, coagulation tests may help to assess the coagulation status. Excessive anticoagulation may require interruption of Dabigatran Teva®. Since Dabigatran Teva® is excreted predominantly by the renal route, adequate diuresis must be maintained.

As protein binding is low, Dabigatran Teva® can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Dabigatran Teva® 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[1,2,9]

For situations when rapid reversal of the anticoagulant effect of Dabigatran Teva® 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 nonactivated) or recombinant Factor VIIa may be taken into account. However, clinical data are very limited.

## Dabigatran Teva® PATIENT SAFETY INFORMATION CARD AND COUNSELING

Please provide your patient the Patient Safety Information card.

The patient should be instructed to carry the Patient Safety Information card at all times and present it when seeing a health care provider.

The patient should be informed about the need for compliance and signs of bleeding and when to seek medical attention.

## REPORTING OF SUSPECTED ADVERSE REACTIONS

Side effects can be reported to the Ministry of Health using the online form for side effect reporting that is found in the Ministry of Health homepage:

www.health.gov.il

or via the link:

https://sideeffects.health.gov.il

or through the registration holder Teva Israel Ltd via:

safety.israel@teva.co.il

## More information

Teva Israel Ltd. P.O.B 3190 124 Dvora HaNevi'a St. Tel Aviv, Israel. Phone: 1-800-805-005

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