Oral Anticoagulant Medication Guide

Coumadin®
Pradaxa®
Xarelto®
Eliquis®
Savaysa®
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In 1954, Coumadin® (warfarin sodium) was introduced as an oral anticoagulant and continues to be widely prescribed to treat various medical conditions. Warfarin is also known as a Vitamin K Antagonist (VKA) since it inhibits the synthesis of Vitamin K dependent clotting factors II, VII, IX, and X and the Vitamin K dependent Protein C and Protein S. It is now advisable for the warfarin patient to maintain a consistent Vitamin K diet rather than trying to avoid Vitamin K sources.

Warfarin has nine different tablet strengths (with each tablet scored), allowing for an individualized warfarin dose that is generally administered once daily in the evening. Despite the nine different tablet strengths, it is generally recommended not to prescribe more than two different tablet strengths since this helps reduce dosing errors. Warfarin continues to rely on the INR laboratory result to guide its dosing.

Warfarin has a significant number of drug interactions that can influence warfarin metabolism and the INR laboratory result. It is recommended that all medication changes [i.e., new medication (acute or chronic), discontinued medication, or dosing strength adjustment (increase/decrease) of an existing medication] be communicated. Warfarin dosing is minimally influenced by renal function. Hepatic function is important to know since hepatic impairment can also potentiate the response to warfarin.

Coumadin® (warfarin sodium) will be further described on page 12 of this medication guide.
**NOAC (New Oral Anticoagulant) Medications**

This newer group of agents is known as NOACs (New/Novel Oral Anticoagulants). The acronym TSOACs (Target Specific Oral Anticoagulants) has also been used. Although a patient’s hepatic function may need to be taken into consideration, these NOACs are greatly influenced by a patient’s renal function, the medications on a patient’s profile (i.e., potential drug interactions) and certain patient characteristics.

In 2010, Pradaxa® (dabigatran etexilate) was initially marketed in the United States as an alternative to warfarin. This new class of medication does not currently require laboratory test monitoring for dosing adjustments and does not require a patient to be maintained on a consistent Vitamin K diet (as seen with warfarin administration). Dabigatran represents a new class of anticoagulants known as oral direct thrombin inhibitors (DTI).

In 2011, another oral anticoagulant-rivaroxiban (Xarelto®) was marketed in the United States as an oral anti-Xa agent. In 2012, apixaban (Eliquis®), a second anti-Xa agent came to the United States market. And in early 2015, a third oral anti-Xa agent edoxaban (Savaysa®) became available. These newer agents are ‘fixed dose’ medications since there are only specified dosing regimens and they are administered on a set schedule either once daily or twice daily rather than an ‘adjusted dose’ regimen seen with a warfarin patient (i.e., individualized dose) based on the INR laboratory test.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa® (dabigatran etexilate)</td>
<td>Oral Direct Thrombin Inhibitor</td>
</tr>
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<td>Xarelto® (rivaroxaban)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Savaysa® (edoxaban)</td>
<td>Oral anti-Xa Inhibitor</td>
</tr>
</tbody>
</table>

**Patient Characteristics**

There are certain patient characteristics that need to be taken into account when selecting and appropriately dosing a NOAC. These characteristics are:

- Age ≥ 80 years
- Body Weight ≤ 60 kg
- Serum Creatinine ≥ 1.5mg/dL (renal function)
- Hepatic Function
Black Box Warning

Thrombotic Events/Stroke
Discontinuing a NOAC in a patient without adequate continuous anticoagulation may increase the risk of thrombotic events and/or stroke. Consider appropriate coverage with another anticoagulant when a NOAC is intermittently or permanently stopped.

Spinal/Epidural Hematoma
Patients currently anticoagulated or scheduled to be anticoagulated are at a risk of developing an epidural or spinal hematoma when undergoing neuraxial anesthesia or spinal puncture. This may result in long term or permanent paralysis.

FDA Approved Indications

The NOACs are currently prescribed for certain FDA approved indications and these indications can vary among each of the NOACs. The use of a NOAC is not indicated in a patient with a prosthetic heart valve. Please consult the FDA approved prescribing information for each individual NOAC.

Renal Impairment

It is very important to know the patient’s renal function lab values and estimated Creatinine Clearance (CrCl). The CrCl is necessary when selecting and appropriately dosing a NOAC. It is also important to periodically assess the patient’s renal function and make note of any CrCl value changes since this may have an impact on a patient’s NOAC dosing regimen. Any CrCl value changes may then necessitate a change in NOAC selection and dosing.

The patient’s Creatinine Clearance (CrCl), along with a concomitantly prescribed medication, may influence the NOAC selection and appropriate dosing.

Listed below is a commonly used Creatinine Clearance formula for adults (Cockroft-Gault).

Please note that certain clinical characteristics such as obesity may warrant the adjustment of the patient’s body weight used in these calculations.

Cockroft-Gault Estimated Creatinine Clearance (CrCl) Formula:

(Reference: Cockroft DW and Gault MH, Nephron, 1976, 16:31-41)

Male = \([140 - \text{age}] \times \text{ABW (kg)} / [72 \times \text{Scr}]\)

Female = Male x 0.85

Note: Use of actual body weight (ABW) in obese patients (and possibly patients with ascites) may significantly overestimate creatinine clearance. Some clinicians prefer to use an adjusted body weight (AdjBW) in such cases [e.g., AdjBW = IBW + 0.4 (ABW-IBW)].

IBW = Ideal Body Weight
Scr = serum creatinine

Dosage and Administration

When a NOAC is to be prescribed, the patient should have an updated and complete medication list including all prescriptions, over the counter (OTC) medications and herbal supplements. The prescriber should then review for potential drug interactions so the appropriate NOAC and dosing regimen is selected.

Conversely, when a patient has already been prescribed a NOAC but is now to be prescribed a new medication (prescription, OTC or herbal), a review process should be followed to determine if there are any drug interactions with the NOAC. Any drug interactions may warrant a NOAC dosage adjustment or even the NOAC being discontinued.

Drug Interactions

NOACs are becoming more recognized by both prescribers and patients as therapeutic options to warfarin. Laboratory tests are currently not needed for this fixed dose NOAC dosing regimens and a consistent Vitamin K diet is not mandatory. However, the patient should still be appropriately screened for potential drug interactions. Certain medication combinations can influence the NOAC’s metabolism and either increase the NOAC drug serum level or decrease the NOAC drug serum level.

Inhibitors

In this context, inhibitors are medications that can “inhibit the metabolism” of a NOAC and increase the NOAC’s drug serum level. This can potentially lead to increased bleeding and/or bruising.

Inducers

In this same context, inducers are medications that can “induce the metabolism” of a NOAC and decrease the NOAC’s drug serum level. This can potentially increase the chance of thrombosis (e.g., blood clot).

Other Anticoagulants

Medications such as aspirin, non-steroidal anti-inflammatory agents (NSAIDs), and other anticoagulants can have an additive anticoagulant effect with concomitantly prescribed NOAC; therefore, the potential exists for an increased bleeding risk.
Clotting Cascade

The following diagram is known as the ‘Clotting Cascade’ and illustrates the coagulation factors that are impacted by warfarin (VKA), dabigatran (DTI) and the oral anti-Xa agents (rivaroxaban, apixaban and edoxaban).

Institute for Safe Medication Practices (ISMP)

The Institute for Safe Medication Practices (ISMP) has developed a list of “High-Alert Medications” on [http://www.ismp.org/tools/highalertmedications.pdf](http://www.ismp.org/tools/highalertmedications.pdf) that includes medications with a heightened risk of causing significant patient harm when they are used in error. This list does not mean that mistakes are more common but it does emphasize that the consequences of an error would be more devastating to a patient. The above referenced list was published in 2012 and updated in 2014 to include all currently FDA approved NOACs.
**SBAR Communication for Coumadin® (warfarin sodium)**

**SITUATION -**
The patient's International Normalized Ratio (INR) is NOT within the intended INR range (i.e., the INR is considered either SUB-therapeutic or SUPRA-therapeutic).

**BACKGROUND -**
There are many variables that can affect the warfarin dose and INR. If a patient has an unstable or erratic INR, the patient's warfarin dosing may need to be adjusted and/or the patient's INR may need to be drawn more frequently.

**ASSESSMENT -**
The INR may NOT be within the intended INR range due to less than optimal warfarin dosing, potential drug interactions with warfarin, potential interactions with Vitamin K sources, and an appropriate frequency or scheduled frequency of obtaining INR lab values.

**RECOMMENDATION -**
If the INR is not consistently within the prescribed INR range, consider rechecking the INR more frequently and also consider adjusting the warfarin dose so that there is an almost same daily dose of warfarin.

If a new medication is prescribed (short term acute medication or long term maintenance medication), determine if there is a potential warfarin drug interaction and then recheck the INR within 3 to 7 days of when that new medication is initiated.

If a patient's warfarin dose has been established and the INR has been stable, but a medication with a potential warfarin drug interaction has been discontinued, recheck the INR within (3 to 7 days) of when the new medication has been discontinued.

If a patient's warfarin dose has been established and the INR has been stable, but a medication with a potential warfarin drug interaction has had its dosage strength either increased or decreased, recheck the INR within 3 to 7 days of when this dosage change has taken place.

If Vitamin K sources from either dietary sources (e.g., food) or supplements (e.g., enteral feedings, multivitamins) are initiated or discontinued, consider checking the INR more frequently.
# Coumadin® (warfarin sodium) SBAR Form

Report to a physician a SUB-therapeutic/SUPRA-therapeutic INR.

<table>
<thead>
<tr>
<th>S</th>
<th>SITUATION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I am calling about (name of patient).</td>
<td></td>
</tr>
<tr>
<td>• The patient’s INR is ___</td>
<td></td>
</tr>
<tr>
<td>• The patient's target INR range is (2.0 - 3.0), (2.5-3.5), or ___ and the above reported INR is considered SUB-therapeutic/SUPRA-therapeutic</td>
<td></td>
</tr>
<tr>
<td>• The patient IS/IS NOT experiencing bruising</td>
<td></td>
</tr>
<tr>
<td>• The patient IS/IS NOT experiencing bleeding</td>
<td></td>
</tr>
<tr>
<td>• The patient HAS/HAS NOT fallen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>BACKGROUND:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The patient is allergic to the following medications:</td>
<td></td>
</tr>
<tr>
<td>• The patient HAS/HAS NOT had Heparin Induced Thrombocytopenia (HIT)</td>
<td></td>
</tr>
<tr>
<td>• The patient HAS/DOES NOT HAVE a mechanical valve (Mitral/Aortic)</td>
<td></td>
</tr>
<tr>
<td>• Table (I) Quick Reference Guide and Table (II) Potential Drug Interactions (see Appendix) with warfarin have been reviewed.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>ASSESSMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ___The INR may be the result of a missed or held warfarin dose</td>
<td></td>
</tr>
<tr>
<td>• ___The INR may be the result of a potential drug interaction with warfarin</td>
<td></td>
</tr>
<tr>
<td>• ___The INR may be the result of a Vitamin K (dietary or supplement) source</td>
<td></td>
</tr>
<tr>
<td>• ___The INR may be the result of a concomitant illness such as: diarrhea, fever, hepatic disorder, nutritional status and/or CHF exacerbation</td>
<td></td>
</tr>
<tr>
<td>• ___Other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>RECOMMENDATIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><strong>It is determined that a potential drug interaction may exist between warfarin sodium (Coumadin®) and</strong></em>_____________________:</td>
<td></td>
</tr>
<tr>
<td>o The new medication may ELEVATE the patient’s INR with the next INR to be drawn: <em><strong>/</strong>/</em>__</td>
<td></td>
</tr>
<tr>
<td>o The new medication may DECREASE the patient's INR with the next INR to be drawn: <em><strong>/</strong>/</em>__</td>
<td></td>
</tr>
<tr>
<td>o The new medication is CONTRAINDICATED with warfarin and should NOT be dispensed</td>
<td></td>
</tr>
<tr>
<td>_<strong>The INR warrants administration of ___ mg of oral Vitamin K1 (phytonadione) with the next INR to be drawn: <em><strong>/</strong>/</em></strong></td>
<td></td>
</tr>
<tr>
<td>_<strong>The INR warrants administration of Heparin or Low Molecular Weight Heparin (LMWH) ‘bridge’ with the next INR to be drawn: <em><strong>/</strong>/</em></strong></td>
<td></td>
</tr>
<tr>
<td>_<strong>No change to the warfarin regimen. The next INR is to be drawn: <em><strong>/</strong>/</em></strong>.</td>
<td></td>
</tr>
<tr>
<td><em><strong>Hold the warfarin dose as follows (specify dates):</strong></em>_________________________<strong>. The next INR to be drawn: <em><strong>/</strong>/</em></strong></td>
<td></td>
</tr>
<tr>
<td>_<strong>Change the warfarin regimen to ______________________ with the next INR to be drawn: <em><strong>/</strong>/</em></strong></td>
<td></td>
</tr>
<tr>
<td>___The situation warrants transportation to an Emergency Room for further evaluation and/or treatment.</td>
<td></td>
</tr>
<tr>
<td>___Other</td>
<td></td>
</tr>
</tbody>
</table>

Evaluated by Nursing Supervisor: ___________________________ Date: / / 
Evaluated by Dispensing Pharmacist: ___________________________ Date: / / 
Evaluated by Physician: ___________________________ Date: / /
SBAR Communication for NOAC (New Oral Anticoagulant) Medications

**SITUATION** - The patient is to be prescribed one of the following medications:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa® (dabigatran etexilate)</td>
<td>Oral Direct Thrombin Inhibitor</td>
</tr>
<tr>
<td>Xarelto® (rivaroxaban)</td>
<td>Oral anti-Xa Inhibitor</td>
</tr>
<tr>
<td>Eliquis® (apixaban)</td>
<td>Oral anti-Xa Inhibitor</td>
</tr>
<tr>
<td>Savaysa® (edoxaban)</td>
<td>Oral anti-Xa Inhibitor</td>
</tr>
</tbody>
</table>

**BACKGROUND** – There are certain patient characteristics (e.g., age, body weight, renal function, hepatic function) that need to be taken into account when selecting and appropriately dosing a NOAC. The patient’s creatinine clearance (CrCl), along with a concomitantly prescribed medication, may influence the NOAC selection and appropriate dosing.

**ASSESSMENT** – Listed below is a commonly used creatinine clearance formula to assist in appropriate NOAC selection and dosing.

**Cockroft-Gault Estimated Creatinine Clearance (CrCl) Formula:**
(Reference: Cockroft DW and Gault MH, Nephron, 1976, 16:31-41)

\[
\begin{align*}
\text{Male} & = \frac{([140 - \text{age}] \times \text{ABW} \text{ (kg)})}{[72 \times \text{Scr}]} \\
\text{Female} & = \text{Male} \times 0.85
\end{align*}
\]

**Note:** Use of actual body weight (ABW) in obese patients (and possibly patients with ascites) may significantly overestimate creatinine clearance. Some clinicians prefer to use an adjusted body weight (AdjBW) in such cases [e.g., AdjBW = IBW + 0.4 (ABW-IBW)].

IBW=ideal Body Weight Scr=serum creatinine

**RECOMMENDATION** – The NOACs are currently prescribed for certain FDA approved indications and these indications can vary among each of the NOACs. Please consult the FDA approved prescribing information for each individual NOAC. **When a NOAC is to be prescribed the patient’s renal function and CrCl must be determined.** In addition, the patient should have an updated and complete medication list including all prescriptions, over the counter (OTC) medications and herbal supplements.

The prescriber should review for potential drug interactions so the appropriate NOAC and dosing regimen is selected. Conversely, when a patient has already been prescribed a NOAC, but is now to be prescribed a new medication (prescription, OTC or herbal), a review process should be followed to determine if there are any drug interactions with the NOAC. Any drug interaction may warrant a NOAC dosage adjustment or even the NOAC being discontinued.
# SBAR NOAC (New Oral Anticoagulant) Form

**SITUATION:** Prescribing a NOAC  
- I am calling about (Name of Patient):
- The patient is to be prescribed (select only ONE of the following):
  - Pradaxa® *(dabigatran etexilate)*
  - Xarelto® *(rivaroxaban)*
  - Eliquis® *(apixaban)*
  - Savaysa® *(edoxaban)*
- Is the patient currently on anticoagulant(s)? (e.g., warfarin, heparin, low-molecular weight heparin (enoxaparin, fondaparinux) or any antiplatelet agent (e.g. aspirin, non-steroidal anti-inflammatory drugs, Plavix®, Effient®, Brilinta®)? If so, list: ____________________________ INR____ aPTT____
  - Date of last test ______________________
- Are any of the patient’s current anticoagulants/antiplatelets to be discontinued prior to the NOAC started? _____. For how many days?
- Is the patient undergoing neuraxial anesthesia or a spinal puncture? ____

**BACKGROUND:**
- The patient’s age is _____. Is the patient’s age ≥ 80 years? _____.
- The patient’s weight is _____. Is the patient’s weight ≤ 60 kg? _____.
- The Patient’s Serum Creatinine is _____. Is the patient’s Scr ≥ 1.5 mg/dL? _____.
- Does the patient have Hepatic dysfunction? ______
- As per the FDA approved prescribing information for the NOAC, have any drug interactions been identified? _______________________________.  
  If so, what are those medication(s)? ___________________________.

**ASSESSMENT:**
- Patient’s BMI: _____.
- Is the patient considered obese? _____. If so, has obesity been adjusted for (and accounted for) in the CrCl formula? ______.
- What is the patient’s CrCl? _____. Date of calculation: _____.

**RECOMMENDATIONS:**
- Does the patient have an FDA approved indication for the NOAC being prescribed? _____.  
  What is that indication? ___________________________.
- Has the patient’s medication list been updated and reviewed for potential drug interactions with the NOAC? (e.g., prescription, OTC, herbal)

**Decision:**
- There is a CONTRAINDICATION between the NOAC and a medication on the patient’s medication profile; therefore, the NOAC should NOT be dispensed.
- The patient’s CrCl is _________. As per the FDA approved prescribing information, the NOAC is CONTRAINDICATED due to renal dysfunction; therefore, the NOAC should NOT be dispensed.
- The patient’s CrCl, medication list and patient characteristics have been reviewed and it is determined that the NOAC ____________________ (name) be prescribed at the following dose: _____________________________.

Evaluated by Nursing Supervisor: ____________________________ Date:  ___/___/___
Evaluated by Dispensing Pharmacist: ____________________________ Date:  ___/___/___
Evaluated by Physician: ____________________________ Date:  ___/___/___
**Coumadin® (warfarin sodium) Monograph**

**Coumadin® (warfarin sodium)**
Source: Coumadin® US Full Prescribing Information (Revised: 10/2011)

- FDA approved since 1954
- Inhibits the synthesis of Vitamin K-dependent clotting factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S
- Scored Tablets: 1mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7.5mg and 10mg tablets
- For Injection: Vial containing 5mg lyophilized powder

**Black Box Warning (Bleeding Risk):**
See Coumadin® US Full Prescribing Information for the complete boxed warning

- Coumadin can cause major or fatal bleeding. See Coumadin® Prescribing Information (Section 5.1)
- Perform regular monitoring of INR in all treated patients. See Coumadin® Prescribing Information (Section 2.1)
- Drugs, dietary changes, and other factors affect INR levels achieved with Coumadin Therapy. See Coumadin® Prescribing Information (Section 7)
- Instruct patients about prevention measures to minimize risk of bleeding and to report signs and symptoms of bleeding. See Coumadin® Prescribing Information (Section 17)

**FDA Approved Indications:**
Source: Coumadin® Prescribing Information (Section 1)

- Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE)
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement
- Reduction in the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after myocardial infarction

**Limitations of Use:**
Coumadin has no direct effect on an established thrombus, nor does it reverse ischemic tissue damage. Once a thrombus has occurred, however, the goals of anticoagulant treatment are to prevent further extension of the formed clot and to prevent secondary thromboembolic complications that may result in serious and possibly fatal sequelae.
<table>
<thead>
<tr>
<th><strong>Absorption/Metabolism/Elimination:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Coumadin® Prescribing Information (Section 12)</td>
</tr>
<tr>
<td>• Absorption: Peak concentration generally attained within the first 4 hours (See Section 12.3)</td>
</tr>
<tr>
<td>• Metabolism: Coumadin is a racemic mixture of the R- and S- enantiomers of warfarin. The S-enantiomer exhibits two to five times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. (See Section 12.3)</td>
</tr>
<tr>
<td>• Elimination: Almost entirely metabolized by cytochrome P-450 enzymes to inactive metabolites</td>
</tr>
<tr>
<td>• Pharmacogenomics: CYP2C9 and VKORC1 Polymorphisms. (See Section 12.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Renal Impairment:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Coumadin® Prescribing Information (Section 8.6)</td>
</tr>
</tbody>
</table>

Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal impairment.

<table>
<thead>
<tr>
<th><strong>Hepatic Impairment:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Coumadin® Prescribing Information (Section 8.7)</td>
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</tbody>
</table>

Hepatic impairment can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin. Use caution when using Coumadin® in these patients.

<table>
<thead>
<tr>
<th><strong>Dosage and Administration:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Coumadin® Prescribing Information (Section 2)</td>
</tr>
<tr>
<td>• Individualized Dosing. See Coumadin® Prescribing Information (Section 2.1)</td>
</tr>
<tr>
<td>• Recommended Target INR Ranges and Durations for Individual Indications. See Coumadin® Prescribing Information (Section 2.2)</td>
</tr>
<tr>
<td>• Initial and Maintenance Dosing. See Coumadin® Prescribing Information (Section 2.3)</td>
</tr>
<tr>
<td>• Monitoring to Achieve Optimal Anticoagulation. See Coumadin® Prescribing Information (Section 2.4)</td>
</tr>
<tr>
<td>• Missed Dose. See Coumadin® Prescribing Information (Section 2.5)</td>
</tr>
<tr>
<td>• Intravenous Route of Administration. See Coumadin® Prescribing Information (Section 2.6)</td>
</tr>
<tr>
<td>• Treatment during Dentistry and Surgery. See Coumadin® Prescribing Information (Section 2.7)</td>
</tr>
<tr>
<td>• Conversion from Other Anticoagulants. See Coumadin® Prescribing Information (Section 2.8)</td>
</tr>
</tbody>
</table>
Drug Interactions:
Source: Coumadin® Prescribing Information (Section 7)

- Consult labeling of all concurrently used drugs for complete information about interactions with Coumadin or increased risks for bleeding. See Coumadin® Prescribing Information (Section 7)
- Inhibitors and Inducers of CYP2C9, 1A2, or 3A4: May alter warfarin exposure. Monitor INR closely when any such drug is used with Coumadin. See Coumadin® Prescribing Information (Section 7.1)
- Drugs that Increase Bleeding Risk: Closely monitor patients receiving any such drug (e.g., other anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory drugs, serotonin reuptake inhibitors). See Coumadin® Prescribing Information (Section 7.2)
- Antibiotics and Antifungals: Closely monitor INR when initiating or stopping an antibiotic or antifungal course of therapy. See Coumadin® Prescribing Information (Section 7.3)
- Botanical (Herbal) Products: Some may influence patient response to Coumadin necessitating close INR monitoring. See Coumadin® Prescribing Information (Section 7.4)

Contraindications:
Source: Coumadin® Prescribing Information (Section 4)

- Pregnancy, except in women with mechanical heart valves. See Coumadin® Prescribing Information (Section 4)
- Hemorrhagic tendencies or blood dyscrasias. See Coumadin® Prescribing Information (Section 4)
- Recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces. See Coumadin® Prescribing Information (Section 4 and Section 5.7)
- Bleeding tendencies associated with certain conditions. See Coumadin® Prescribing Information (Section 4)
- Threatened abortion, eclampsia, and preeclampsia. See Coumadin® Prescribing Information (Section 4)
- Unsupervised patients with potential high levels of non-compliance. See Coumadin® Prescribing Information (Section 4)
- Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. See Coumadin® Prescribing Information (Section 4)
- Hypersensitivity to warfarin or any component of the product. See Coumadin® Prescribing Information (Section 4)
- Major regional or lumbar block anesthesia. See Coumadin® Prescribing Information (Section 4)
- Malignant hypertension. See Coumadin® Prescribing Information (Section 4)
### Warnings and Precautions:
Source: Coumadin® Prescribing Information (Section 5)

- Hemorrhage. See Coumadin® Prescribing Information (Section 5.1)
- Tissue Necrosis. See Coumadin® Prescribing Information (Section 5.2)
- Systemic Atheroemboli and Cholesterol Microemboli. See Coumadin® Prescribing Information (Section 5.3)
- Heparin Induced Thrombocytopenia. See Coumadin® Prescribing Information (Section 5.4)
- Use in Pregnant Women with Mechanical Heart Valves. See Coumadin® Prescribing Information (Section 5.5)
- Females of Reproductive Potential. See Coumadin® Prescribing Information (Section 5.6)
- Other Clinical Settings with Increased Risks. See Coumadin® Prescribing Information (Section 5.7)
- Endogenous Factors Affecting the INR. See Coumadin® Prescribing Information (Section 5.8)

### Adverse Reactions:
See Coumadin® Prescribing Information (Section 6)

Most common adverse reactions to Coumadin are fatal and nonfatal hemorrhage from any tissue or organ.

### Patient Counseling Information
Source: Patient Counseling Information (Section 17)

- Report any falls, bruising or bleeding to your physician
- Strictly adhere to your dosing schedule
- Carry identification stating that you are on Coumadin®
- Obtain blood tests (prothrombin time (PT), INR) regularly as recommended by your doctor
- Eat a normal, balanced diet to maintain a consistent Vitamin K intake. Avoid drastic changes in the amount of dark, leafy green vegetables eaten
- Report any serious illness such as severe diarrhea, infection or fever to your doctor
- If the prescribed dose of Coumadin® is missed, take the dose as soon as possible on the same day but do not take a double dose the next day to make up for missed doses
# Pradaxa® (dabigatran etexilate) Monograph

**Pradaxa® (dabigatran etexilate)**

*Source: Pradaxa® US Full Prescribing Information (Revised: 04/2014)*


- FDA approved since October 2010
- Competitive, direct thrombin inhibitor (DTI)
- Prodrug dabigatran etexilate metabolized to active drug dabigatran
- 75mg & 150mg capsule strengths
- Twice daily administration
- Adverse effects mostly GI related

## Black Box Warning:

*Source: Pradaxa® Prescribing Information (Revised: 04/2014)*

**Thrombotic Events/Stroke**

Premature discontinuation *increases the risk of thrombotic events*. If anticoagulation is discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

**Spinal/Epidural Hematoma**

- Epidural or spinal hematomas have occurred in patients receiving neuraxial anesthesia or undergoing spinal puncture while on Pradaxa®
- May result in long term or permanent paralysis
- Optimal timing between the administration of Pradaxa® and neuraxial procedures is not known

## FDA Approved Indications:

*Source: Pradaxa® Prescribing Information (Section 1)*

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with parenteral anticoagulant for 5-10 days
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated
Absorption/Metabolism/Elimination:
Source: Pradaxa® Prescribing Information (Section 12.3)

- Absorption: Onset of action (max concentration) is one – two hours. Oral bioavailability increases by 75 percent when pellets are taken without the capsule shell compared to the intact capsule formulation; therefore, Pradaxa® capsules should NOT be broken, chewed, or opened before administration.
- Metabolism: After oral administration, dabigatran etexilate is converted to dabigatran. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Hepatic impairment showed large inter-subject variability with moderate hepatic impairment but no evidence of a consistent change in exposure or pharmacodynamics.
- Elimination: Primarily excreted in the urine (renal) and feces.
- Dabigatran is not a substrate, inhibitor, inducer of the CYP450 enzymes. Source: Pradaxa® Prescribing Information (Section 12.3)

Renal Impairment:

- Dosing recommendations for patients with CrCl<15ml/min or on dialysis cannot be provided. See Pradaxa® Prescribing Information (Section 8.6, dosing (Section 2), and drug interactions (Section 7) for additional information.

Dosage and Administration:
Source: Pradaxa® Prescribing Information (Section 2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing Risk of Stroke and Systemic Embolism in Non-valvular AF</td>
<td></td>
</tr>
<tr>
<td>CrC1 &gt; 30 mL/min:</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>CrC1 15 to 30 mL/min:</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>CrC1 &lt; 15 mL/min or on dialysis:</td>
<td>Dosing recommendations can’t be provided</td>
</tr>
<tr>
<td>CrC1 30 to 50 mL/min with concomitant use of P-gp inhibitors:</td>
<td>Consider reducing dose to 75 mg twice daily if given with P-gp dinedarone or ketocomazole. Dose adjustment is not necessary when co-administered with other P-gp inhibitors</td>
</tr>
<tr>
<td>CrC1 &lt; 30 mL/min with concomitant use of P-gp inhibitors:</td>
<td>Avoid co-administration</td>
</tr>
</tbody>
</table>

| Treatment of DVT and PE                                                  | 150 mg twice daily |
| Reduction in the Risk of Recurrence of DVT and PE                       | Dosing recommendations cannot be provided                             |
| CrC1 > 30 mL/min:                                                       | 150 mg twice daily |
| CrC1 < 30 mL/min or on dialysis:                                        | Dosing recommendations cannot be provided                             |
| CrC1 < 30 mL/min or on dialysis:                                        | Avoid co-administration |
| CrC1 < 50 m:/min with concomitant use of P-gp inhibitors                | Avoid co-administration |
Converting from/to Warfarin:
Source: Pradaxa® Prescribing Information (Section 2.4)

- When converting patients FROM warfarin TO Pradaxa®, discontinue warfarin and start Pradaxa when the INR is below 2.0
- When converting FROM Pradaxa® TO warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
  - For CrCl ≥ 50ml/min, start warfarin three days before discontinuing Pradaxa®
  - For CrCl 30-50ml/min, start warfarin two days before discontinuing Pradaxa®
  - For CrCl 15-30ml/min, start warfarin one day before discontinuing Pradaxa®
  - For CrCl < 15ml/min, no recommendations can be made

Converting from/to Parenteral Anticoagulant:
Source: Pradaxa® Prescribing Information (Section 2.5)

- For patients currently receiving a parenteral anticoagulant, start Pradaxa® (0 to 2 hours) before the time that the next dose of the parenteral drug was to have been administered - or at the time of discontinuation of a continuously administered parenteral drug (e.g., IV UFH).
- For patients currently taking Pradaxa®, wait 12 hours (CrCl ≥30mL/min) or 24 hours (CrCl <30mL/min) after the last dose of Pradaxa® before initiating treatment with a parenteral anticoagulant.

Drug Interactions:

Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure
Source: Pradaxa® Prescribing Information (Section 5.5)

- The concomitant use of Pradaxa® with P-gp Inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided [see Clinical Pharmacology (12.3)]
- P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran [see Clinical Pharmacology (12.3)] Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone

Reduction of Risk of Stroke and Systemic Embolism in NVAF
Source: Pradaxa® Prescribing Information (Section 5.5)

- Consider reducing the dose of Pradaxa® to 75mg BID when dronedarone or systemic ketoconazole is coadministered with Pradaxa® in patients with moderate renal impairment (CrCl 30-50 mL/min)
- Avoid use of Pradaxa® and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30mL/min) [see Drug Interactions (7.1) and use in specific populations (8.6)]
Treatment and Reduction in the Risk of Recurrence of DVT & PE
Source: Pradaxa® Prescribing Information (Section 5.5)

- Avoid use of Pradaxa® and concomitant P-gp inhibitors in patients with CrCl < 50mL/min [See Drug Interactions (7.2) and Use in Specific Populations (8.6)]

Source: Pradaxa® Prescribing Information (Section 7.1)

- In patients with moderate renal impairment (CrCl 30-50mL/min), consider reducing the dose of Pradaxa® to 75mg BID when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole
- The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of Pradaxa®. These results should not be extrapolated to other P-gp inhibitors [see Warnings and Precautions (5.4), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]
- The concomitant use of Pradaxa® and P-gp inhibitors with severe renal impairment (CrCl 15-30 mL/min) should be avoided [see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]

Reduction of Risk of Stroke and Systemic Embolism in NVAF (Renal Impairment)
Source: Pradaxa® Prescribing Information (Section 8.6)

- No dose adjustment of Pradaxa® is recommended in patients with mild or moderate renal impairment [see Clinical Pharmacology (12.3)]. Reduce the dose of Pradaxa® in patients with severe renal impairment (CrCl 15-30 mL/min) [see Dosage and Administration (2.1, 2.2) and Clinical Pharmacology (12.3)]. Dosing recommendations for patients with CrCl < 15 mL/min or on dialysis cannot be provided
- Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors [see Warnings and Precautions (5.5), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]

Treatment and Reduction in the Risk of Recurrence of DVT and PE (Renal Impairment)
Source: Pradaxa® Prescribing Information (Section 8.6)

- Patients with severe renal impairment (CrCl < 30mL/min) were excluded from RE-COVER (pre-market clinical trial)
- Dosing recommendations for patients with CrCl < 30mL/min or on dialysis cannot be provided. Avoid use of Pradaxa® with concomitant P-gp inhibitors in patients with CrCl < 50 mL/min [see Warnings and Precautions (5.5), Drug Interactions (7.2), and Clinical Pharmacology (12.3)].
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Source: Pradaxa® Prescribing Information (Section 5.2)

- Anticoagulants and NSAIDs/Aspirin

Source: Pradaxa® Prescribing Information (Section 7.1)

- See Pharmacokinetics/Drug Interactions (Section 12.3)

Discontinuation for Surgery and Other Interventions:
Source: Pradaxa® Prescribing Information (Section 2.6)

Warnings and Precautions:
Source: Pradaxa® Prescribing Information (Section 5)

- Increased Risk of Thrombotic Events after Premature Discontinuation (See Pradaxa® Prescribing Information Section 5.1)
- Risk of Bleeding (See Pradaxa® Prescribing Information Section 5.2)
- Spinal/Epidural Anesthesia or Puncture (See Pradaxa® Prescribing Information Section 5.3)
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves (See Pradaxa® Prescribing Information Section 5.4)
- Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure (See Pradaxa® Prescribing Information Section 5.5)

Patient Counseling Information:
Source: Pradaxa® Prescribing Information (Section 2.3)

- Keep Pradaxa® in the original bottle to protect from moisture.
- Do not put Pradaxa® in pill boxes or pill organizers.
- Swallow Pradaxa® capsules whole with a full glass of water.
- May be administered with or without food.
- Breaking, chewing, or emptying the contents of the Pradaxa® capsule can result in increased exposure.
- If a dose of Pradaxa® is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least six hours before the next scheduled dose.
- The dose of Pradaxa® should NOT be doubled to make up for a missed dose.

Notes:
**Xarelto® (rivaroxaban) Monograph**

**Xarelto® (rivaroxaban)**  
Source: Xarelto® US Full Prescribing Information (Revised: 12/2014)  
Prescribing Information link: [http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100](http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100)

- FDA approved since July 2011  
- Selective, anti-Xa inhibitor  
- 10mg, 15mg, & 20mg tablet strengths  
- Once daily administration

**Black Box Warning:**  
Source: Xarelto® Prescribing Information

**Thrombotic Events/Stroke:** Premature discontinuation increases the risk of thrombotic events. If anticoagulation is discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

**Spinal/Epidural Hematoma**

- Epidural or spinal hematomas have occurred in patients receiving neuraxial anesthesia or undergoing spinal puncture while on Xarelto®  
- May result in long term or permanent paralysis  
- Optimal timing between the administration of Xarelto® and neuraxial procedures is not known

**FDA Approved Indications:**  
Source: Xarelto® Prescribing Information (Section 1)

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)  
- For the treatment of deep vein thrombosis (DVT)  
- For the treatment of pulmonary embolism (PE)  
- For the reduction in the risk of recurrence of DVT and PE  
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery

**Absorption/Metabolism/Elimination:**  
Source: Xarelto® Prescribing Information (Section 12.3)

- Absorption: Onset of action (max concentration) is 2-4 hours  
- Metabolism: Primarily metabolized hepatically by CYP3A4/5 and CYP2J2  
- Elimination: Primarily excreted in the urine (renal) and feces

**Renal Impairment:**  
See Xarelto® Prescribing Information (Section 8.7), dosing (Section 2), and drug interactions (Section 7) for additional information.
Avoid use of Xarelto® in deep vein thrombosis/pulmonary embolism (DVT/PE) if CrCl<30ml/min.

**Hepatic Impairment:**
See Xarelto® Prescribing Information (Section 8.8)

**Dosage and Administration:**
Source: Xarelto® Prescribing Information (see Section 2.0)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in Risk of Stroke in Nonvalvar Atrial Fibrillation (2.3)</strong></td>
<td><strong>CrCl&gt;50 mL/min:</strong> 20 mg once daily with the evening meal</td>
</tr>
<tr>
<td></td>
<td><strong>CrCl 15 to 50 mL/min:</strong> 15 mg once daily with the evening meal</td>
</tr>
<tr>
<td><strong>Treatment of DVT (2.4)</strong></td>
<td>15 mg twice daily with food, for first 21 days</td>
</tr>
<tr>
<td><strong>Treatment of PE (2.4)</strong></td>
<td>▼ after 21 days, transition to ▼</td>
</tr>
<tr>
<td><strong>Reduction in the Risk of Recurrence of DVT and of PE (2.4)</strong></td>
<td>20 mg once daily with food</td>
</tr>
<tr>
<td><strong>Prophylaxis of DVT Following Hip or Knee Replacement Surgery (2.5)</strong></td>
<td>Hip replacement: 10 mg once daily for 35 days</td>
</tr>
<tr>
<td></td>
<td>Knee replacement: 10 mg once daily for 12 days</td>
</tr>
</tbody>
</table>

**Converting from/to Warfarin:**
Source: Xarelto® Prescribing Information (Section 2.2)

**Switching FROM Warfarin TO Xarelto®** – When switching patients from warfarin to Xarelto®, discontinue warfarin and start Xarelto® as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation.

**Switching FROM Xarelto® TO Warfarin** – No clinical trial data are available to guide converting patients from Xarelto® to warfarin. Xarelto® affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue Xarelto® and begin both a parenteral anticoagulant and warfarin at the time the next dose of Xarelto® would have been taken.

**Converting from/to Other Anticoagulants:**
Source: Xarelto® Prescribing Information (Section 2.2)

**Switching from Xarelto® to anticoagulants other than warfarin** – For patients currently taking Xarelto® and transitioning to an anticoagulant with rapid onset, discontinue Xarelto® and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next Xarelto® dose would have been taken [see Drug Interactions (7.3)].
### Switching from Anticoagulants other than Warfarin to Xarelto®

For patients currently receiving an anticoagulant other than warfarin, start Xarelto® (0 to 2 hours) prior to the next scheduled evening administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For UFH being administered by continuous infusion, stop the infusion and start Xarelto® at the same time.

### Drug Interactions:

#### Drugs that Inhibit Cytochrome P450 3A4 Enzymes & Drug Transport Systems

*Source: Xarelto® Prescribing Information (Section 7.1)*

- In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole), increases in rivaroxaban exposure and pharmacodynamics effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30 percent to 160 percent. Significant increases in rivaroxaban exposure may increase bleeding risk [see Clinical Pharmacology (12.3)].
- When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during co-administration with drugs are combined P-gp and CYP3A4 inhibitors.
- Avoid concomitant administration of Xarelto® with combined P-gp and strong CYP3A4 inhibitors [see Warnings and Precautions (5.6)].

#### Drugs that Induce Cytochrome P450 3A4 Enzymes & Drug Transport Systems

*Source: Xarelto® Prescribing Information (Section 7.2)*

- Results from drug interaction studies and population PK analyses from clinical studies indicate co-administration of Xarelto® with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50 percent.
- Similar decreases in pharmacodynamics effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy [see Clinical Pharmacology (12.3)].
- Avoid concomitant use of Xarelto® with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s Wort) [see Warnings and Precautions (5.6)].

#### Anticoagulants and NSAIDs/Aspirin

*Source: Xarelto® Prescribing Information (Section 7.3)*

- Single doses of enoxaparin and Xarelto® given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and Xarelto® resulted in an additive effect on factor Xa (FXa) inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials.
- NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with Xarelto®. Coadministration of the platelet aggregation inhibitor clopidogrel and Xarelto® resulted in an increase in bleeding time for some subjects [see Clinical Pharmacology (12.3)].
- Avoid concurrent use of Xarelto® with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs [see Warnings and Precautions (5.2)].

**Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems**

See Xarelto® Prescribing Information (Section 7.4)

**Discontinuation for Surgery and Other Interventions:**

See Xarelto® Prescribing Information (Section 2.6)

**Warnings and Precautions:**

Source: Xarelto® Prescribing Information (Section 5)

- Increased Risk of Thrombotic Events after Premature Discontinuation (See Xarelto® Prescribing Information Section 5.1)
- Risk of Bleeding (See Xarelto® Prescribing Information Section 5.2)
- Spinal/Epidural Anesthesia or Puncture (See Xarelto® Prescribing Information Section 5.3)
- Use in Patients with Renal Impairment (See Xarelto® Prescribing Information Section 5.4)
- Use in Patients with Hepatic Impairment (See Xarelto® Prescribing Information Section 5.5)
- Use with P-gp and Strong CYP3A4 Inhibitors or Inducers (See Xarelto® Prescribing Information Section 5.6)
- Risk of Pregnancy-Related Hemorrhage (See Xarelto® Prescribing Information Section 5.7)
- Patients with Prosthetic Heart Valves (See Xarelto® Prescribing Information Section 5.8)
- Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy (See Xarelto® Prescribing Information Section 5.9)

**Patient Counseling Information:**

Source: Xarelto® Prescribing Information (Section 17)

- The 15mg and 20mg Xarelto® tablets should be taken with food.
- The 10mg tablet can be taken with or without food.
- In the NVAF clinical study, Xarelto® was taken with the evening meal.
- See Xarelto® Prescribing Information (Section 2.8) for administration options (e.g.,
NG tube, GT tube, crushed tablet administration).

- Missed Dose (See Xarelto® Prescribing Information Section 2.7):
  - Patients on 15mg twice daily: Take missed dose immediately to ensure total daily intake of 30mg per day. Continue regular dosage the next day.
  - Patients on other doses once daily: Take the missed dose as soon as possible on the same day then continue regular dosage the next day.

Notes:
Eliquis® (apixaban) Monograph

**Eliquis® (apixaban)**
Source: Eliquis® US Full Prescribing Information (Revised: 08/2014)
Prescribing information link: [http://packageinserts.bms.com/pi/pi_eliquis.pdf](http://packageinserts.bms.com/pi/pi_eliquis.pdf)

- FDA approved since December 28, 2012
- Selective, anti-Xa inhibitor
- 2.5mg & 5mg tablet strengths
- Twice daily administration

**Black Box Warning:**
Source: Eliquis® Prescribing Information

**Thrombotic Events/Stroke**
Premature discontinuation increases the risk of thrombotic events. If anticoagulation is discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

**Spinal/Epidural Hematoma**
- Epidural or spinal hematomas may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture while on Eliquis®
- May result in long term or permanent paralysis
- Optimal timing between the administration of Eliquis® and neuraxial procedures is not known

**FDA Approved Indications:**
Source: Eliquis® Prescribing Information (Section 1)
- Reduction of risk of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF)
- Prophylaxis of deep vein thrombosis following hip or knee replacement surgery

**Absorption/Elimination/Metabolism:**
Source: Eliquis® Prescribing Information (Section 12.3)
- Absorption: Onset of action (max concentration) is three – four hours
- Metabolism: Metabolized hepatically mainly via CYP3A4
- Elimination: Primarily excreted in the urine (renal) and feces

**Hepatic Impairment:**
See Eliquis® Prescribing Information (Section 2.6)
**Renal Impairment:**
See Eliquis® Prescribing Information (Section 2.7), dosing (Section 2), and drug interactions (Section 7) for additional information.

The dose for NVAF patients with end stage renal disease on hemodialysis is 5mg twice daily. Reduce dose to 2.5mg if >=80 years old or <=60kg.

**Dosage and Administration:**
Source: Eliquis® Prescribing Information (Section 2.1)

Reduction of Risk of Stroke and Systemic Embolism in Patients with NVAF
- The recommended dose of Eliquis for most patients is 5mg BID.

Prophylaxis of DVT following Hip or Knee Replacement Surgery
- The recommended dose of Eliquis® is 2.5mg BID. The initial dose should be taken 12 to 24 hours after surgery.
- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

**Dosage Adjustments:**
Source: Eliquis® Prescribing Information (Section 2.2)

In patients with NVAF, the recommended dose of Eliquis® is 2.5mg BID in patients with any two of the following characteristics:
- Age ≥ 80 years
- Body weight ≤ 60kg
- Serum creatinine ≥ 1.5mg/dL

Source: Eliquis® Prescribing Information (Section 2.2)

Coadministration with CYP3A4 and P-gp Inhibitors:
- For patients receiving Eliquis® 5mg BID when Eliquis® is co-administered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin), the recommended dose is 2.5mg BID [see Clinical Pharmacology (12.3)].
- In patients already taking 2.5mg BID, co-administration of Eliquis® with strong dual inhibitors of CYP3A4 and P-gp should be avoided.

**Converting from/to Warfarin:**
Source: Eliquis® Prescribing Information (Section 2.5)

Switching FROM warfarin TO Eliquis®: Warfarin should be discontinued and Eliquis® started when the INR is below (2.0).

Switching FROM Eliquis TO warfarin: Eliquis® affects INR, so that initial INR measurements
during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue Eliquis® and begin both a parenteral anticoagulant and warfarin at the time the next dose of Eliquis® would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

**Switching between Eliquis® and anticoagulants other than warfarin:** Discontinue one being taken and begin the other at the next scheduled dose.

**Drug Interactions:**
*Source: Eliquis® Prescribing Information (Section 7)*

Apixaban is a substrate of both CYP3A4 and P-gp.

- Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding.
- Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke.

**Strong Dual Inhibitors of CYP3A4 and P-gp**
*Source: Eliquis® Prescribing Information (Section 7.1)*

- For patients receiving 5mg BID, the dose of Eliquis® should be decreased to 2.5mg BID when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].
- In patients already taking Eliquis® at a dose of 2.5mg BID, avoid co-administration with strong dual inhibitors of CYP3A4 and P-gp [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

**Strong Dual Inducers of CYP3A4 and P-gp**
*Source: Eliquis® Prescribing Information (Section 7.2)*

- Avoid concomitant use of Eliquis® with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort) because such drugs will decrease exposure to apixaban [see Clinical Pharmacology (12.3)].

**Anticoagulants and Antiplatelet Agents**
*Source: Eliquis® Prescribing Information (Section 7.3)*

- Co-administration of an antiplatelet agent, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

**Temporary Interruption for Surgery and Other Interventions:**
*See Eliquis® Prescribing Information (Section 2.4)*

**Warnings and Precautions:**
*Source: Eliquis® Prescribing Information (Section 5)*
- Increased Risk of Stroke with Discontinuation of Eliquis® in Patients with Nonvalvular Atrial Fibrillation (NVAF)  (See Eliquis® Prescribing Information Section 5.1)
- Bleeding  (See Eliquis® Prescribing Information Section 5.2)
- Spinal/Epidural Anesthesia or Puncture  (See Eliquis® Prescribing Information Section 5.3)
- Patients with Prosthetic Heart Valves  (See Eliquis® Prescribing Information Section 5.4)

**Patient Counseling Information:**
Source: Eliquis® Prescribing Information Section 2.8, 17

- For patients unable to swallow whole tablets, 5mg and 2.5mg tablets may be crushed and suspended in 60 mL D5W and immediately delivered through nasogastric tube (NGT).
- Information regarding the administration of crushed and suspended Eliquis® tablets swallowed by mouth is not available.
- Can take with or without food.
- If a dose of Eliquis® is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

**Notes:**
# Savaysa® (edoxaban) Monograph

**Savaysa® (edoxaban)**  
Source: Savaysa® US Full Prescribing Information (Revised: 01/2015)  
Prescribing information link: [http://dsi.com/prescribing-information-portlet/getPlContent?productName=Savaysa&inline=true](http://dsi.com/prescribing-information-portlet/getPlContent?productName=Savaysa&inline=true)

- FDA approved since 2015  
- Selective, anti-Xa inhibitor  
- 15mg, 30mg and 60mg tablet strengths  
- Once daily administration

## Black Box Warning:

Source: Savaysa® Prescribing Information

### Renal Function

Reduced efficacy in nonvalvular atrial fibrillation patients with creatinine clearance (CrCl) > 95ml/min

### Thrombotic Events/Stroke

Premature discontinuation increases the risk of ischemic events. If anticoagulation is discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant as described in transition guidance (Sections 2.4, 5.2 and 14.1).

### Spinal/Epidural Hematoma

- Epidural or spinal hematomas may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture while on Savaysa®  
- May result in long term or permanent paralysis  
- Optimal timing between the administration of Savaysa® and neuraxial procedures is not known

## FDA Approved Indications:

Source: Savaysa® Prescribing Information (Section 1)

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF) in patients with CrCl < =95mL/min  
- Treatment of deep vein thrombosis and pulmonary embolism following 5 to 10 days of initial therapy with a parenteral anticoagulant
Absorption/ Metabolism/Elimination:
Source: Savaysa® Prescribing Information (Section 12.3)

- Absorption: Peak plasma edoxaban concentrations observed in 1 to 2 hours
- Metabolism: Predominantly unchanged. Minimal metabolism via hydrolysis
- Elimination: Primarily excreted as unchanged drug in the urine

Renal Impairment:
See Savaysa® Prescribing Information (Section 8.6), dosing (Section 2), and drug interactions (Section 7) for additional information.

Reduce dose to 30mg once daily in patients with CrCl 15-50mL/min. Savaysa® is not recommended if CrCl is <15mL/min.

Hepatic Impairment:
See Savaysa® Prescribing Information (Section 8.7)

The use of Savaysa® in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction required in mild hepatic impairment.

Dosage and Administration:
Source: Savaysa® Prescribing Information (Section 2.1)

Reduction of Risk of Stroke and Systemic Embolism in Patients with NVAF
- The recommended dose of Savaysa® is 60mg once daily in patients with CrCl< = 95 and >50mL/min

Treatment of Deep Vein Thrombosis and Pulmonary Embolism
- The recommended dose of Savaysa® is 60mg once daily following 5 to 10 days of initial therapy with a parenteral anticoagulant

Dosage Adjustments:
Source: Savaysa® Prescribing Information (Section 2.2)

In all patients:
- Reduce dose of Savaysa® to 30mg once daily if CrCl is 15 – 50mL/min
- Avoid concomitant use in patients on rifampin

In treatment of patients for DVT and Pulmonary Embolism, also use 30mg once daily if:
- Patient’s CrCl is 15- 50 ml/min
- Patient’s body weight ≤ 60kg
- Patient is also on certain drugs that are P-gp inhibitors*

*Section 7 of the package insert says that dose reductions are not necessary however, section 2.2 states the following: In some clinical studies, the 30mg dose was used when
patient was also receiving select P-gp inhibitors (e.g. verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or ketoconazole). However package insert also states (in section 7.3) that edoxaban blood levels were lower in these patients therefore no dosage reduction is recommended. Due to this discrepancy, clinical judgement of the medical provider must be used in determining the appropriate dose in such situations.

### Converting from/to Warfarin:

**Source:** Savaysa® Prescribing Information (Section 2.4)

**Switching FROM warfarin TO Savaysa®:** Discontinue warfarin and start Savaysa® when the INR is \( \leq 2.5 \).

**Switching FROM Savaysa® TO warfarin:** Oral option: For patients taking 60mg of Savaysa®, reduce dose to 30mg and begin warfarin concomitantly. Monitor INR at least weekly and draw blood prior to daily dose of Savaysa® to minimize influence on INR value. Once INR is stable and \( \geq 2.0 \), discontinue Savaysa®. If starting dose of Savaysa® is 30mg, reduce dose to 15mg and follow same procedure.

See full prescribing information for parenteral conversion protocol.

**Switching between Savaysa® and non-vitamin K dependent anticoagulants:** Discontinue one being taken and begin the other at the next scheduled dose.

### Drug Interactions:

**Source:** Savaysa® Prescribing Information (Section 7)

**Anticoagulants, Antiplatelets and Thrombolytics**

Co-administration of these agents may increase risk of bleeding. Long term concomitant treatment is not recommended. Promptly evaluate for signs and symptoms of bleeding and/or blood loss.

**P-glycoprotein (P-gp) Inducers**

Avoid the concomitant use of Savaysa® and rifampin.

**P-glycoprotein (P-gp) Inhibitors**

No dose reduction is recommended when Savaysa® is used with P-gp inhibitors.

*See additional comments in "Dosage Adjustments" section above*

### Temporary Interruption for Surgery and Other Interventions:

**Source:** Savaysa® Prescribing Information (Section 2.5)

### Warnings and Precautions:

**Source:** Savaysa® Prescribing Information (Section 5)

- Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl > 95mL/min do not use in these patients
- Premature discontinuation increases the risk of ischemic events. If anticoagulation is
discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant as described in transition guidance (Sections 2.4, 5.2 and 14.1).

- Savaysa® increases the risk of bleeding and can cause serious and potentially fatal bleeding. There is no established way to reverse the effects of Savaysa®, which can persist for approximately 24 hours after the last dose. The effects of Savaysa® cannot be reliably monitored with standard laboratory testing.

- Spinal/Epidural anesthesia or puncture (See Savaysa® Prescribing Information Section 5.4)

- The safety of Savaysa® has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. It’s use is not recommended in these patients

<table>
<thead>
<tr>
<th>Patient Counseling Information:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Savaysa® Prescribing Information Section 17</td>
</tr>
</tbody>
</table>

- You may bruise or bleed more easily and longer when treated with Savaysa®
- Report any unusual bleeding to your health care provider immediately
- Take exactly as prescribed, do not discontinue without talking to healthcare provider
- Inform healthcare provider you are taking Savaysa® before any surgery, medical or dental procedure
- If you have neuraxial anesthesia or spinal puncture watch for signs of adverse effects such as back pain, tingling, numbness, muscle weakness and stool/urine incontinence. Contact physician immediately if these symptoms occur
- If you miss a dose, take Savaysa® as soon as possible on the same day and resume normal dosing schedule the next day. DO NOT double up after a missed dose

Notes:
Appendices

- Table I: Quick Reference Guide – Potential Drug-Drug, Dietary Interactions & Medical Conditions with Coumadin® (warfarin sodium)
- Table II: Potential Drug-Drug Interactions with Coumadin® (warfarin sodium)

The information contained in this guide is intended for educational purposes only and is not a substitute for professional clinical judgment. The information contained within is condensed. Please refer to the latest full prescribing information and additional reference materials for the most complete and up to date information. Quality Insights is not responsible for any omissions or errors. This document is not intended to override a clinician’s judgment in individual patient management.
TABLE I: Quick Reference Guide
Revised 4/18/2012
Potential Drug-Drug, Dietary Interactions & Medical Conditions with Coumadin® (warfarin sodium)

The following medications have documented Drug-Drug Interactions with Warfarin sodium; therefore, the INR must be monitored appropriately whenever these medications are INITIATED, DOSE ADJUSTED, or DISCONTINUED. Please note that this is NOT a complete list of Drug-Drug, Dietary Interactions & Medical Conditions but intended to be an INITIAL Quick Reference. Please see Table (II) for more information.

<table>
<thead>
<tr>
<th>Medications/Dietary/Medical Conditions that can ELEVATE the INR [↑]</th>
<th>Medications/Dietary/Medical Conditions that can REDUCE the INR [↓]</th>
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</thead>
<tbody>
<tr>
<td>Medications: (F-A-M-E-S) Achronym</td>
<td>Medications:</td>
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<tr>
<td>- Fluconazole</td>
<td>- Antacids</td>
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<tr>
<td>- Fenofibrate</td>
<td>- Carbamazepine</td>
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<tr>
<td>- Amiodarone</td>
<td>- Cholestyramine</td>
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<tr>
<td>- Metronidazole</td>
<td>- Multivitamins (which contains Vit K)</td>
</tr>
<tr>
<td>- Erythromycin</td>
<td>- Phenobarbital</td>
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<tr>
<td>- Sulfur Based (i.e, Bactrim)</td>
<td>- Rifampin</td>
</tr>
<tr>
<td>Medications (miscellaneous):</td>
<td>- Sucralfate</td>
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<tr>
<td>- Antibiotics</td>
<td>Dietary Interactions/Medical Conditions:</td>
</tr>
<tr>
<td>- NSAIDs</td>
<td>- Enteral Feedings (conc. of Vit K/rate)</td>
</tr>
<tr>
<td>- Omeprazole</td>
<td>- Olean®</td>
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<tr>
<td>- SSRIs</td>
<td>- Smoking (increased)</td>
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<tr>
<td>- Statins</td>
<td>- Vegetable Oils</td>
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<tr>
<td>- Steroids</td>
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<tr>
<td>- Valproic Acid</td>
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<tr>
<td>Dietary Interactions/Medical Conditions:</td>
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<tr>
<td>- Anise</td>
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<td>- Black licorice</td>
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<td>- CHF exacerbation</td>
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<tr>
<td>- Diarrhea</td>
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<td>- Fever</td>
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<tr>
<td>- Hepatic Disorders</td>
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</tbody>
</table>

‡ Please note that this is NOT a complete list but intended to be an INITIAL Quick Reference. Each medication that is prescribed, dose adjusted, or discontinued should be evaluated for potential Drug-Drug Interactions with warfarin sodium. Please consult the labeling of all concurrently used medications to obtain further drug interaction information.
TABLE II: Potential Drug-Drug Interactions with Coumadin® (warfarin sodium)
Revised 4/18/2012

The following medications have documented Drug-Drug Interactions with warfarin sodium; therefore, the INR must be monitored appropriately whenever these medications are INITIATED, DOSE ADJUSTED, or DISCONTINUED.

The following are examples of Cytochrome P-450 (2C9, 1A2, 3A4) Interactions with warfarin sodium.* This list should NOT be considered all-inclusive. Please consult the labeling of all medications to obtain further drug interaction information.

<table>
<thead>
<tr>
<th>INHIBITORS</th>
<th>INDUCERS</th>
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<tbody>
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<td><strong>Inhibit the Metabolism of Warfarin</strong></td>
<td><strong>Induce the Metabolism of Warfarin</strong></td>
</tr>
<tr>
<td>(ELEVATE ↑ INR)</td>
<td>(REDUCE ↓ INR)</td>
</tr>
<tr>
<td>acyclovir</td>
<td>amprenavir (can also ↑ INR)</td>
</tr>
<tr>
<td>allopurinol</td>
<td>aprepitant (can also ↑ INR)</td>
</tr>
<tr>
<td>alprazolam</td>
<td>armodafinil</td>
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<td>amiodarone</td>
<td>bosentan</td>
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<tr>
<td>amlodipine</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>ampicillin (can also ↓ INR)</td>
<td>cigarette smoking</td>
</tr>
<tr>
<td>aprepitant (can also ↓ INR)</td>
<td>efavirenz</td>
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<tr>
<td>atazanavir</td>
<td>etravirine (can also ↑ INR)</td>
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<td>atorvastat</td>
<td>modafinil</td>
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<td>bicalutamide</td>
<td>montelukast</td>
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<td>nafcillin</td>
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<td>nifedipine</td>
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<td>nizatidine</td>
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<td>cyclosporine</td>
<td>omeprazole</td>
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<tr>
<td>darunavir/ritonavir</td>
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<td>diltiazem</td>
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<td>prednisone</td>
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<td>enoxacin</td>
<td>rifampin</td>
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<tr>
<td>erythromycin</td>
<td>rufinamide</td>
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<tr>
<td>etravirine (can also ↓ INR)</td>
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<tr>
<td>famotidine</td>
<td>saquinavir</td>
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<tr>
<td>isoniazid</td>
<td>sulfonylureas</td>
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<td>terbinafine</td>
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<tr>
<td>lopinavir/ritonavir</td>
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<td>tipranavir</td>
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<td>vandetanib</td>
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<tr>
<td>nefazodone</td>
<td>voriconazole</td>
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**Inhibit the Metabolism of Warfarin**

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<td>zafirlukast</td>
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<td>zileuton</td>
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<td>fosamprenavir</td>
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<tr>
<td>imatinib</td>
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<tr>
<td>indinavir</td>
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**Induce the Metabolism of Warfarin**

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