Eliquis®

(apixaban) tablets 5mg 2.5mg

Dosing Guide

for All ELIQUIS Indications

Find out more at

hcp.eliquis.com

ELIQUIS® (apixaban) INDICATIONS

Approved for 6 indications

to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)

for the treatment of deep vein thrombosis (DVT)

for the treatment of pulmonary embolism (PE)

to reduce the risk of recurrent DVT and PE following initial therapy

for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip replacement surgery

for the prophylaxis of DVT, which may lead to PE, in patients who have undergone knee replacement surgery

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

ELIQUIS® (apixaban) DOSING SUMMARY

Indication	Recommended dosing
For all indications: Please see page 15 for additional dosage adjustment information on coadministration with combined P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors.	
 **Reduction in the risk of stroke/systemic embolism in NVAF**	5 mg twice daily in most patients **Dose adjustment for NVAF patients:** 2.5 mg twice daily is recommended for patients with at least 2 of the following characteristics: • age ≥80 years • body weight ≤60 kg • serum creatinine ≥1.5 mg/dL
 **Treatment of DVT/PE**	10 mg twice daily for the first 7 days ▼ After 7 days, transition to ▼ 5 mg twice daily
 **Reduction in the risk of recurrent DVT/PE following initial therapy**	2.5 mg twice daily after at least 6 months of treatment for DVT or PE
 **Prophylaxis of DVT, which may lead to PE, following hip or knee replacement surgery**	2.5 mg twice daily for 35 days starting 12 to 24 hours after hip replacement surgery 2.5 mg twice daily for 12 days starting 12 to 24 hours after knee replacement surgery

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

Please see additional Important Safety Information throughout. Please see full Prescribing Information including **Boxed WARNINGS** and Medication Guide or visit ELIQUIS.com.

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For patients with NVAF, DOSING FOR REDUCING THE RISK OF STROKE & SYSTEMIC EMBOLISM

5 mg taken orally twice daily recommended for most NVAF patients

5 mg twice daily

Recommended dose

In 2 Phase III NVAF clinical trials, approximately 95% of ELIQUIS® (apixaban) patients received this dose.

2.5 mg twice daily

Dosage adjustment

Patients with **at least 2** of the following:

- **a** age ≥80 years
- **b** body weight ≤60 kg
- **c** serum creatinine ≥1.5 mg/dl

PLEASE SEE PAGES 8-16 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily, recommended for the treatment of DVT and PE

Recommended dose

10 mg (two 5 mg tablets) twice daily

Day 1 to Day 7

5 mg twice daily

Following Day 7

An example of an ELIQUIS® (apixaban) prescription for a patient starting therapy for the treatment of DVT/PE

FOR _____

ADDRESS _____

℞

ELIQUIS 5 mg tablets

Take 2 tablets by mouth twice daily for 7 days

Followed by 1 tablet by mouth twice daily

First 30 days = 74 tablets

Subsequent prescriptions for a 30-day supply = 60 tablets (take one 5 mg tablet by mouth twice daily)

PLEASE SEE PAGES 8-16 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.

For patients who have experienced a DVT/PE, REDUCING THE RISK OF RECURRENT DVT/PE FOLLOWING INITIAL THERAPY

2.5 mg taken orally twice daily recommended for the reduction in the risk of recurrent DVT/PE following initial therapy

Recommended dose

2.5 mg twice daily

Following ≥6 months of treatment for DVT or PE

Reduce dose by 50%: For patients receiving ELIQUIS® (apixaban) doses of **5 mg or 10 mg twice daily,** when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir).
Clarithromycin
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

In patients already taking ELIQUIS at a dose of 2.5 mg twice daily: Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Bleeding Risk** (continued)
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.

For patients who have undergone hip or knee replacement surgery, DOSING FOR PROPHYLAXIS OF DVT, WHICH MAY LEAD TO PE

2.5 mg taken orally twice daily recommended for hip or knee replacement surgery patients

Recommended dose

2½ 2.5 mg twice daily

The initial dose should be taken 12 to 24 hours after hip or knee replacement surgery

35 DAYS Recommended treatment duration for patients undergoing **hip replacement surgery**

12 DAYS Recommended treatment duration for patients undergoing **knee replacement surgery**

In patients already taking ELIQUIS® (apixaban) at a dose of 2.5 mg twice daily: Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors.
Clarithromycin
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

PLEASE SEE PAGES 8-16 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

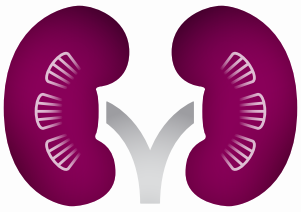
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

DOSING IN PATIENTS WITH RENAL IMPAIRMENT

ELIQUIS® (apixaban) elimination



Renal excretion accounts for about **27%** of total clearance

- ELIQUIS is eliminated in both urine and feces. Biliary and direct intestinal excretion contributes to elimination of ELIQUIS in the feces

Dosing Considerations in NVAF Patients With Renal Impairment

Renal impairment	No dose adjustment
Mild	✓
Moderate	✓
Severe	✓

No dose adjustment for renal impairment *alone* in patients with NVAF (see page 9 for additional dosage adjustment criteria)

Patients with end-stage renal disease (ESRD) on dialysis:

- Clinical efficacy and safety studies with ELIQUIS® (apixaban) did not enroll patients with ESRD on dialysis
- In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study
- It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as were seen in ARISTOTLE

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

Please see additional Important Safety Information throughout. Please see full Prescribing Information including **Boxed WARNINGS** and Medication Guide or visit ELIQUIS.com.

Eliquis® (apixaban) tablets 5mg 2.5mg

Dosing Considerations in NVAF Patients With Renal Impairment

5 mg taken orally twice daily recommended for most NVAF patients

5 mg twice daily

Recommended dose

In 2 Phase III NVAF clinical trials, approximately 95% of ELIQUIS® (apixaban) patients received this dose.

2.5 mg twice daily

Dosage adjustment

Patients with **at least 2** of the following:

- **a** age ≥80 years
- **b** body weight ≤60 kg
- **c** serum creatinine ≥1.5 mg/dl

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

DOSING IN PATIENTS WITH RENAL IMPAIRMENT

Dosing considerations in patients with renal impairment for all other ELIQUIS® (apixaban) indications

No dose adjustment is recommended for patients with renal impairment, including those with end-stage renal disease (ESRD) on dialysis, for the following indications:

Prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery

Treatment of DVT

Treatment of PE

Reduction in the risk of recurrent DVT and PE following initial therapy

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis.

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

DOSING IN PATIENTS WITH HEPATIC IMPAIRMENT

Dosing in patients with hepatic impairment

Mild hepatic impairment (Child-Pugh class A)	**Moderate** hepatic impairment (Child-Pugh class B)	**Severe** hepatic impairment (Child-Pugh class C)
No dose adjustment required	There is limited clinical experience with ELIQUIS® (apixaban) in patients with moderate hepatic impairment; dosing recommendation cannot be provided	ELIQUIS is not recommended

Adjust ELIQUIS dose for patients taking drugs that are combined P-gp and strong CYP3A4 inhibitors.

See Drug Interactions on page 15 for more information.

SELECTED IMPORTANT SAFETY INFORMATION

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DOSING CONSIDERATIONS AND ADMINISTRATION OPTIONS

Additional dosing considerations

- Does not require routine monitoring using international normalized ratio (INR) or other tests of coagulation
- No known dietary restrictions
- Can be taken with or without food
- **Missed dose**: If a dose of ELIQUIS® (apixaban) 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

Temporary interruption for surgery and other interventions[1]

Bleeding risk with elective surgery or invasive procedures	Recommendation
Moderate or **high risk** of unacceptable or clinically significant bleeding	Discontinue ELIQUIS at least **48 hours** prior
Low risk or **noncritical site** and **easily controlled**	Discontinue ELIQUIS at least **24 hours** prior

- Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

Guidance for switching patients to and from ELIQUIS® (apixaban)

Switching from anticoagulants other than warfarin (oral or parenteral) to ELIQUIS

- Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin

Switching from ELIQUIS to anticoagulants other than warfarin (oral or parenteral)

- Discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS

Switching from ELIQUIS to warfarin

- ELIQUIS affects INR, so that initial INR measurements during transition to warfarin may not be useful for determining the appropriate dose of warfarin
- One approach is to discontinue ELIQUIS and begin both parenteral anticoagulant and warfarin at the time the next dose would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range

Switching from warfarin to ELIQUIS

- Discontinue warfarin and start ELIQUIS when the INR is < 2.0

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (continued)

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.

ADMINISTRATION OPTIONS[1]

- For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS® (apixaban) tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally
- Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube
- Crushed ELIQUIS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (continued)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

DRUG INTERACTIONS

Combined P-gp and strong CYP3A4 inhibitors Ketoconazole Itraconazole Ritonavir	**Reduce dose by 50%:** For patients receiving ELIQUIS® (apixaban) doses of **5 mg or 10 mg twice daily** when coadministered with combined P-gp and strong CYP3A4 inhibitors **In patients already taking ELIQUIS at a dose of 2.5 mg twice daily:** • Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors **These drugs increase exposure to ELIQUIS and increase the risk of bleeding**
Clarithromycin	**PK data suggest that no dose adjustment is necessary**
Combined P-gp and strong CYP3A4 inducers Rifampin Phenytoin Carbamazepine St. John's wort	**Avoid concomitant use.** **These drugs decrease exposure to ELIQUIS and increase the risk of stroke and other thromboembolic events.**

PK=pharmacokinetic.
These drug categories are examples described in the Full Prescribing Information, not an all-inclusive list.

SELECTED IMPORTANT SAFETY INFORMATION

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Drugs affecting hemostasis

Coadministration with these drugs increases the risk of bleeding:

- Aspirin and other antiplatelet agents
- Other anticoagulants
- Heparin
- Thrombolytic agents
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), when used chronically
- Fibrinolytics

These drug categories are examples described in the Full Prescribing Information, not an all-inclusive list.

Additional considerations

- Apixaban is a substrate of both CYP3A4 and P-gp
- Famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of ELIQUIS® (apixaban) in healthy subjects
- ELIQUIS did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid in healthy subjects
- APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo
- For diltiazem, no dose adjustment of ELIQUIS is required[2]

ELIQUIS® (apixaban): CONSIDERATIONS FOR REVERSING THE ANTICOAGULANT EFFECTS[1]

An agent to reverse the anti-factor Xa activity of ELIQUIS is available

- Please visit www.andexxa.com for more information on availability of a reversal agent

The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, ie, for about two drug half lives

Additional information for reversal of anticoagulant effect

- Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies
- When PCCs are used, monitoring for the anticoagulation effect of ELIQUIS using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended
- Hemodialysis does not appear to have a substantial impact on ELIQUIS exposure
- Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of ELIQUIS
- There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving ELIQUIS
- There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving ELIQUIS, and they are not expected to be effective as a reversal agent

Activated oral charcoal reduces absorption of ELIQUIS, thereby lowering ELIQUIS plasma concentration

aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time.

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Approved for 6 Indications

Find out more at:
hcp.eliquis.com

References: 1. ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.
2. Data on File. APIX075. Bristol-Myers Squibb Company, Princeton, NJ.

Please see full Prescribing Information including **Boxed WARNINGS** and Medication Guide or visit ELIQUIS.com.