Apixaban (Eliquis®)

Classification:

AHFS Therapeutic Class: 20.12.04 Anticoagulant
Apixaban (Eliquis®) is a direct oral anticoagulant (DOAC) medication used in the treatment and prevention of thrombotic events**.**

Pharmacology:

Apixaban is a reversible selective competitive inhibitor of Factor Xa. Apixaban's mechanism involves inhibition of prothrombinase activity. The result is a decrease in thrombin activation and decrease in thrombus formation.

Indication -FDA & literature supported non-FDA

FDA Labeled Indications (FDA Approval Dec. 28th, 2012):

- Arthroplasty of the knee: post-operative deep vein thrombosis (DVT) prophylaxis (px)
- Atrial fibrillation (nonvalvular) – cerebrovascular accident; embolism px
- DVT treatment
- DVT: recurrence px
- Total hip replacement: post-operative DVT px
- Pulmonary embolism (PE) treatment
- PE, recurrence px

Off-label Indications:

- Heparin-induced thrombocytopenia (HIT)

Pharmacokinetics

Pharmacokinetic Parameter	Details
Elimination Half-life	15.2 hours (5mg) 6.8 h (2.5mg) Low Body wt: 15.8 h Obesity: 8.8 h
Bioavailability (Oral)	50% (whole, crushed-oral, crushed-nasogastric)

Pharmacokinetic Parameter	Details
Metabolism	Primarily CYP3A4 Substrate of CYP3A4 and P-glycoprotein
Tmax	3-4 h (10mg) 3.3 h (5mg) 1.5 h (2.5mg)
Food Effects	High fat meal: Whole tablet: Tmax increase by 1 hour Crushed Tablets: Cmax decrease 20%, AUC decrease 16%
Protein Binding (Albumin)	Most patients: 87% Hemodialysis: 92-94%
Volume of distribution (Vd)	Most Patients: 21-61 L Low body wt: 52.7 L Obesity: 75.6 L
Excretion	Majority: fecal biliary (mostly unchanged) Renal: 27% (mostly unchanged) Dialysis: 4% removed in 4h Total body clearance: 82.3 mL/min low body weight 68.8mL/min obesity 106.8 mL/min

Dosage / Administration

- Nonvalvular Atrial Fibrillation Embolism px: most patients→ 5 mg orally twice daily (see Dosage Adjustments)
- Post-operative (knee or hip) DVT px: 2.5 mg twice daily beginning 12-24 hours after surgery; hip surgery treatment duration is 35 days. Knee surgery treatment duration is 12 days.
- PE/DVT treatment: 10 mg taken orally twice daily for the first 7 days. Following 7 days, reduce dose to 5 mg orally twice daily.
- DVT/PE: recurrence px: The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE
- Missed dose: 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.

- Temporary interruption for surgery/other intervention: 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 non-critical 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.

Dosage Adjustments

- Geriatric:
  - Nonvalvular Atrial Fibrillaation Embolism px meeting at least 2/3 of the following criteria: Age ≥ 80 years, body weight ≤ 60 kg, and/or serum creatinine ≥ 1.5 mg/dL→ use alternate dose: 2.5 mg orally twice daily
- Renal:
  - Nonvalvular Atrial Fibrillaation Embolism px meeting at least 2/3 of the following criteria: Age ≥ 80 years, body weight ≤ 60 kg, and/or serum creatinine ≥ 1.5 mg/dL→ use alternate dose: 2.5 mg orally twice daily
  - DVT/PE px or treatment: No Adjustment
- Dialysis:
  - DVT/PE px or treatment: No Adjustment
  - Stroke prevention: 2.5 mg orally twice daily
- Hepatic:
  - Mild (Child-Pugh class A): No Adjustment
  - Severe (Child-Pugh class C): Not Recommended
- Combined P-glycoprotein and strong CYP3A4 inhibitor:
  - Decrease dose by 50% in patients receiving more than 2.5 mg twice daily
  - Patients already on 2.5 mg twice daily: AVOID

Use in Special Population

- Pregnancy - fetal risk cannot be ruled out. Use during labor/delivery in patients receiving neuraxial anesthesia increases risk of epidural hematoma.
- Lactation - Not recommended; there is no current data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and metabolites were present in the milk of treated rats.
- Geriatrics – avoid in elderly patients with renal clearance below 25 mL/min
- Pediatrics - Safety and efficacy not established in pediatric patients

- Renal Dysfunction - may require dose adjustment in atrial fibrillation
- Hepatic Dysfunction – no adjustment in mild impairment. Avoid in severe impairment (Child-Pugh class C)

Contraindication

- Patients with active pathological bleeding
- Patients with severe hypersensitivity/anaphylaxis reactions to apixaban

Boxed Warning

- Premature discontinuation of apixaban or any oral anticoagulant increases the risk of thrombotic events. Consider an alternative anticoagulant if apixaban treatment is discontinued for any reason other than pathological bleeding or treatment completion.
- In patients undergoing neuraxial anesthesia or spinal procedure, epidural or spinal hematoma risk is increased and could result in long term or permanent paralysis. The optimal timing between dosing apixaban and neuraxial procedures is unknown. Monitor patients for signs and symptoms of neurologic impairment and treat urgently. Consider the benefits and risk of neuraxial intervention in patients who are or need to be anticoagulated.

Precautions

- Beer's Criteria: avoid use in elderly with CrCl < 25 mL/min due to increased bleeding risk
- If traumatic epidural or spinal puncture occurs, delay administration for 48 hours
- Prosthetic heart valves: the use of DOAC medication is not recommended
- Concomitant use with P-glycoprotein and strong CYP3A4 inducers (Ex: rifampin, carbamazepine, phenytoin, St. John's wort)
- Concomitant use with P-glycoprotein and strong CYP3A4 inhibitors (Ex: ketoconazole, itraconazole, ritonavir)
- Elective procedures: procedures bearing a risk of bleeding may require interruption in therapy beginning 48 hours prior when the risk of bleeding is moderate to high, or 24 hours prior if the bleeding risk is low.
- Exercise caution in patients with postoperative indwelling catheters. Do not remove earlier than 24 hours following the last apixaban dose.
- Serious and potentially fatal bleeding can occur, particularly with concomitant use of other medications that affect hemostasis (Ex: aspirin, antiplatelets, NSAIDs, SSRI, SNRI, thrombolytics, other anticoagulants)

- Anticoagulation may persist for 24 hours beyond the last apixaban dose. Activated charcoal reduces absorption. An anti-factor Xa reversal agent is available.
- Severe hepatic impairment: Use is not recommended
- ESRD requiring dialysis, advanced age (≥80 years old), low body weight (≤ 60 kg): dose adjustment may be necessary
- PE in the setting of hemodynamic instability, as well as patients who may require thrombolysis or pulmonary embolectomy: use not recommended

Sentinel Event Advisory: SEA #61 (Effective July 1st, 2019)

- Create name awareness of the various DOACs among providers, including pharmacists, emergency department (ED) clinicians, and others who may be called on to deal with life-threatening bleeding problems.
- Use evidence-based protocols and practice guidelines for drug initiation and maintenance, anticoagulation reversal, management of bleeding events, and perioperative management for each DOAC.
- Have a written policy in place requiring baseline and ongoing lab tests to monitor and adjust anticoagulant therapy.
- Each particular DOAC's indications for use should be included on the patient's prescription, in instructions for the patient, and in the electronic medical record.
- Address anticoagulation safety practices by evaluating them and setting goals to improve measures, and establishing a process to identify, respond to, and report adverse drug events.
- Provide education to patients and families about the anticoagulant medication prescribed, including adherence to medication dose and schedule, follow-up appointments, potential drug-drug interactions (and interactions with herbs or supplements), the potential for adverse drug reactions and how to spot them, and when to contact a physician or visit the ED.

Adverse Effects

- **Common Adverse Effects (≥ 10%)**: Hemorrhage (overall ≤ 15%; major ≤ 2%, clinically relevant non-major bleeding 4%)
- **Common Adverse Effects (≥ 1%)**: contusion, bleeding gums, hematoma, hematuria, rectal hemorrhage, nausea, menorrhagia, epistaxis, hemoptysis
- **Undefined frequency**: Cardiovascular: Thrombosis (with premature discontinuation)
- Central nervous system: Epidural intracranial hemorrhage (in patients receiving neuraxial anesthesia or undergoing spinal puncture)

- Hematologic & oncologic: Spinal hematoma (in patients receiving neuraxial anesthesia or undergoing spinal puncture)

Monitoring

- Monitoring – Anticoagulation monitoring is not required. However, it provides utility in trauma, urgent procedures/interventions, major bleeding, overdose/suicide attempt, potential interaction, acute thrombosis, liver/renal failure, or adherence verification.
- High risk patients: HAS-BLED risk score (**H**ypertension, **A**bnormal renal and liver function, **S**troke, **B**leeding, **L**abile INRs, **E**lderly, and **D**rugs/alcohol.

Drug-Drug Interactions

- Defibrotide **(CONTRAINDICATED):** increased bleed risk
- P-glycoprotein and Strong CYP3A4 inducers **(MAJOR):** decreased apixaban levels, thrombotic risk *(Examples: rifampin, carbamazepine, phenytoin, St. John's wort)*
- Strong CYP3A4 inhibitors **(MAJOR):** increased apixaban levels, bleeding risk *(Examples: ketoconazole, itraconazole, ritonavir)*
- Fibrinolytics **(MAJOR):** increased bleed risk
- Anticoagulant/antiplatelet agents **(MAJOR):** increased bleed risk

Efficacy

ADVANCE Trials:

Double blind non-inferiority efficacy comparison of apixaban versus enoxaparin in the prophylaxis of deep vein thrombosis following hip or knee replacement surgery. 11,659 patients were randomized in three trials. In all 3 trials, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period.

ADVANCE 1 determined apixaban to be non-inferior to enoxaparin in the primary endpoint. ADVANCE 2 & 3 found apixaban to be superior at meeting the primary endpoints. In all three trials, there were no significant differences in clinically significant bleeding.

Figure 1. ADVANCE 1 & 2 Trial Results

Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			ADVANCE-2		
Events during 12-day treatment period	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE†/All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT‡	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT‡	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

† Total VTE includes symptomatic and asymptomatic DVT and PE.

‡ Includes symptomatic and asymptomatic DVT.

Figure 2. ADVANCE 3 Trial Results

Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

*Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

†Total VTE includes symptomatic and asymptomatic DVT and PE.

‡Includes symptomatic and asymptomatic DVT.

AMPLIFY and AMPLIFY-EXT Trials:

AMPLIFY and AMPLIFY-EXT trials examined the safety and efficacy of apixaban for the treatment of DVT and PE, and for risk reduction of recurrent DVT and PE following 6 to 12 months of treatment. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. In AMPLIFY, the primary objective of non-inferiority to

enoxaparin/warfarin for the incidence of recurrent VTE was met. Randomization included 5244 and 2482 patients respectively. Apixaban was determined to be non-inferior to warfarin/enoxaparin.

AMPLIFY-EXT compared two doses of apixaban against placebo, 2.5 mg twice daily and 5 mg twice daily. The primary endpoint was met, concluding that both doses were superior to placebo.

Figure 3. AMPLIFY Trial Results

Efficacy Results in the AMPLIFY Study

	ELIQUIS N=2609 n	Enoxaparin/Warfarin N=2635 n	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).

† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Figure 4. AMPLIFY-EXT Trial Results

Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	ELIQUIS 2.5 mg bid N=840	ELIQUIS 5 mg bid N=813	Placebo N=829	ELIQUIS 2.5 mg bid vs Placebo	ELIQUIS 5 mg bid vs Placebo
		n (%)			
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

*Patients with more than one event are counted in multiple rows.

ARISTOTLE Trial:

ARISTOTLE trial compared the efficacy of apixaban versus warfarin in preventing thromboembolic event in patients with non-valvular atrial fibrillation. Participants met one or more of the following criteria: prior stroke/TIA, prior embolism, ≥75 years of age, medically managed hypertension, heart failure (≥NYHA Class 2), left ventricular ejection fraction ≤ 40%. A total of 18,201 patients were randomized and followed for an average of 89 weeks.

Apixaban proved superior to warfarin at reducing risk of stroke or embolism. Apixaban was also associated with fewer major bleeds when compared with warfarin.

Figure 5. ARISTOTLE Trial Results

Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	Warfarin N=9081 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

Current Formulary Options / Alternatives

- Fondaparinux (Arixtra®)
- Enoxaparin sodium (Lovenox®)
- Heparin sodium
- Rivaroxaban (Xarelto®)
- Warfarin sodium (Jantoven®,Coumadin®)

Dosage Forms / Cost

Brand only: Eliquis® 2.5 mg oral tablet, 5 mg oral tablet, & 30 day DVT/PE Starter Pack (5 mg oral tablet)

Pharmacoeconomics: Comparison with alternative, rivaroxaban (Xarelto®): Note pricing data is based on retail claims analyzed by goodrx and wellrx, as well as wholesaler pricing data from November 2019. This pricing data is subject to constant fluctuation and should be reviewed on a case-case basis. Pricing is based on one month supply at maintenance doses and may not reflect induction dosing.

- Goodrx (outpatient):
  - Apixaban Medicare Part D copay range: $19-521; goodrx coupon: $448

    - Rivaroxaban Medicare Part D copay range: $19-523; goodrx coupon: $452
- Wellrx (lowest cash price in zip code 78223):
    - Apixaban: $446.59 (HEB)
    - Rivaroxaban: $450.39 (HEB)
- Pharmacy Cost through wholesaler:
    - Apixaban: $426 (awp $538)
    - Rivaroxaban: $430 (awp $533)

Cost Comparison Conclusion: When treating DVT/PE, both medications require an induction dose that could result in partial bottles. The cost difference between the two comparators is not significant factor for inpatient treatment. However, for patients with insurance coverage, or anticipated discharge, the preferred agent on a patient's insurance formulary may influence the selection after clinical factors have been considered.

Special Considerations

Toxicity

- **Acute Ingestion of Toxic dose:** Activated charcoal can be administered if suspicion of recent potentially toxic dose. Seek immediate medical attention. (can be administered prior to hospital)
- **Reversal Agent**: Recombinant Factor Xa (Andexxa®) (to be administered in hospital)

Special Considerations

- Switching from warfarin to apixaban: discontinue warfarin and initiate apixaban when INR is below 2
- Switching from apixaban to warfarin: discontinue apixaban and start warfarin at the time of the next apixaban dose would have been due. At the start of warfarin, bridge with a parenteral anticoagulant until the INR is in therapeutic range.
- Switching from apixaban to anticoagulant other than warfarin (oral or parenteral). Discontinue apixaban and initiate the alternative at the time the next apixaban dose would have been due.
- Switching from anticoagulant (oral or parenteral) other than warfarin to apixaban. Discontinue anticoagulant and initiate apixaban at the time the next dose would have been due.
- Surgery (when procedure site protocol is unspecified) Discontinue apixaban 48 hours prior to procedures with a moderate to high risk of clinically significant bleeding. Discontinue 24 hours prior to procedures with a low

bleed risk or where bleeding could be easily controlled. Bridging is generally not required. Resume apixaban following the procedure, when the patient is hemodynamically stable.

Summary/Conclusion

Apixaban is a DOAC medication indicated for the treatment and prevention of thrombotic events. Use of any anticoagulant agent is accompanied by a risk of bleeding. However, apixaban offers a reasonable side effect profile for patients requiring anticoagulation. The advent of not requiring constant lab monitoring may offset the current price difference between alternative agents. The oral dosage form and recent approval of a reversal agent further promote its utility.

Recommendation

Apixaban should be added to the formulary.

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