Apixaban (Eliquis®)

FDA-Labeled Indication: Non-valvular atrial fibrillation–thromboembolic prophylaxis and treatment

Apixaban Dosing			
Indication	**Dosing Condition**		**Dose**
Non-valvular A-Fib	Any 2 of the following: Age ≥80 years Body weight ≤60 kg Serum creatinine ≥1.5 mg/dL	No drug interactions	2.5 mg PO BID
		ESRD on hemodialysis	2.5 mg PO BID
		Drug interactions: CYP3A4 and P-gp inhibitors: see interactions below	Avoid use
	Normal dosing		5 mg PO BID
	Patients with ESRD on hemodialysis who do not fit above criteria		5 mg PO BID
	Drug interactions: CYP3A4 and P-gp inhibitors: ketoconazole, itraconazole, ritonavir, clarithromycin		2.5 mg PO BID
DVT/PE Treatment	Normal dosing		10 mg PO BID x 7 days, followed by 5 mg PO BID x 6 months
	Drug interactions: CYP3A4 and P-gp inhibitors		5 mg PO BID x 7 days, followed by 2.5 mg PO BID x 6 months
Post-op prophylaxis-Knee replacement[a] and Hip replacement[b]	Normal dosing		2.5 mg PO BID
	Drug interactions: CYP3A4 and P-gp inhibitors: ketoconazole, itraconazole, ritonavir, clarithromycin		Avoid use

a. Start at least 12-24 hrs after surgery and continue for 12 days.
b. Start at least 12-24 hrs after surgery and continue for 35 days.

Hepatic Adjustment:
Moderate or Severe (Child-Pugh B or C), or any hepatic disease associated with coagulopathy: no dosing recommendations available and avoid use.

Drug Interactions:
Strong Dual Inhibitors of CYP3A4 and P-gp: ketoconazole, itraconazole, ritonavir, clarithromycin
Strong Dual Inducers of CYP3A4 and P-gp: rifampin, phenytoin, carbamazepine, St. John's Wort

Hold before surgery:
Procedures with moderate/high risk of bleeding: 48 hours
Procedures with low risk of bleeding: 24 hours

Spinal/Epidural Anesthesia or Puncture:
Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after last administration of apixaban. The next dose of apixaban should not be administered earlier than 5 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of apixaban for 48 hours.

Monitoring:
Monitor for signs of bleeding.

Administration:
Give with or without food.
Enteral tubes: may give via nasogastric tube by crushing and suspending tablet in 60 ml of 5% dextrose solution; administer immediately.

Missed Dose:
Take dose as soon as possible on the same day as the missed dose. For BID dosing, if it is less than 6 hours until the next scheduled dose, skip dose and resume with next dose as scheduled.

Transitioning to or from Apixaban	
Change	**Directions**
Apixaban to warfarin[a]	Discontinue apixaban and start parenteral anticoagulant and warfarin when the next apixaban dose would have been given[b]
Warfarin to apixaban	Discontinue warfarin, and initiate apixaban when INR < 2.0
Apixaban to non-warfarin anticoagulant[c]	Discontinue apixaban and start non-warfarin anticoagulant at the next scheduled dose of apixaban
Non-warfarin anticoagulant to apixaban[c]	Discontinue non-warfarin anticoagulant and start apixaban at the next scheduled dose of non-warfarin anticoagulant
Heparin infusion to apixaban	Discontinue infusion and start apixaban at the same time

a. Apixaban affects INR and measurements during co-administration with warfarin may not be useful to determine the appropriate warfarin dose.
b. Parenteral anticoagulants: enoxaparin, fondaparinux, and subcutaneous heparin. General recommendation is to begin LMWH or UFH with warfarin until INR is clinically appropriate.
c. Enoxaparin, fondaparinux, subcutaneous heparin, rivaroxaban, and dabigatran.

Holding Anticoagulants and Antiplatelets Before Surgery		
Medication		**How long to hold before surgery**
Anticoagulants	warfarin (Coumadin®)	4-5 days
	dabigatran (Pradaxa®)	CrCl ≥ 50 mL/min: 1-2 days CrCl < 50 mL/min: 3-5 days Consider longer time for major surgery, spinal puncture, or placement of spinal/epidural catheter or port
	rivaroxaban (Xarelto®)	24 hours
	apixaban (Eliquis®)	Procedures with high risk of bleeding: 48 hours Procedures with low risk of bleeding: 24 hours
Antiplatelets	clopidogrel (Plavix®)[a]	5 days
	prasugrel (Effient®)[a]	7 days
	ticagrelor (Brilinta®)	5 days[b]

a. Bare metal stent placed within 6 weeks, or drug eluting stent within past 6 months: continue if possible.
b. After 3 days of holding ticagrelor, platelet inhibition approximates platelet inhibition after holding clopidogrel for 5 days.

Reversal of dabigatran, rivaroxaban, and apixaban:
For more information, see policy: 15318 Reversal of Anticoagulants.

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Direct Oral Anticoagulants

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Dabigatran (Pradaxa®)

FDA Labeled Indication: Non-valvular atrial fibrillation– thromboembolic prophylaxis and treatment

Dabigatran Dosing			
Indication	**CrCl (mL/min)**	**Drug Interactions**	**Dose**
Non-valvular A-Fib	> 30	None	150 mg PO BID
	30-50	P-gp inhibitor: ketoconazole, itraconazole, dronedarone, quinidine	75 mg PO BID
	15-30	None	75 mg PO BID
	< 30	P-gp inhibitor: ketoconazole, itraconazole, dronedarone, quinidine	Avoid co-administration
	< 15 or dialysis	None	Dosing recommendations not provided
Treatment of DVT/PE[a] and recurrent DVT/PE	> 30	None	150 mg PO BID
	< 50	P-gp inhibitor: ketoconazole, itraconazole, dronedarone, quinidine	Avoid co-administration
	≤ 30 or dialysis	None	Dosing recommendations not provided
DVT/PE prophylaxis-THR[b]	> 30	None	110 mg on Day 1, then 220 mg x 28-35 days thereafter
	< 50	P-gp inhibitor: ketoconazole, itraconazole, dronedarone, quinidine	Avoid co-administration
	≤ 30 or dialysis	None	Dosing recommendations not provided

a. After treatment with parenteral therapy for 5-10 days.
b. First dose given 1-4 hours after total hip replacement (THR) surgery when patient is at hemostasis. If dabigatran is not started until the day after surgery, initiate treatment with 220 mg once daily.

Drug Interactions:
P-gp inhibitors: ketoconazole, itraconazole, dronedarone, quinidine
Avoid use with P-gp inducers: rifampin

Hold before invasive or surgical procedures:
CrCl ≥ 50 mL/min: 1-2 days
CrCl < 50 mL/min: 3-5 days
Consider longer time for major surgery, spinal puncture, or placement of spinal/epidural catheter or port.

Monitoring:
Monitoring during bleeds:
Thrombin Time: normal level excludes the presence of dabigatran. Less useful in overdose; thrombin time is elevated in the presence of drug but is not sensitive to the degree of anticoagulation.

Administration:
Give with or without food.
Swallow whole. Do no crush, chew or empty contents of capsule.

Missed Dose:
Take dose as soon as possible on the same day as the missed dose. If it is less than 6 hours until the next scheduled dose, skip dose and resume with next dose as scheduled.

Transitioning to or from Dabigatran		
Change	**Directions**	
Dabigatran to warfarin[a]	CrCl ≥50 mL/min	Start warfarin 3 days before discontinuing dabigatran
	CrCl 30-50 mL/min	Start warfarin 2 days before discontinuing dabigatran
	CrCl 15-30 mL/min	Start warfarin 1 day before discontinuing dabigatran
	CrCl <15 mL/min	No recommendations can be made
Warfarin to dabigatran	Discontinue warfarin and start dabigatran when INR is below 2.0	
Dabigatran to parenteral anticoagulant[b]	CrCl ≥30 mL/min	Wait 12 hrs after last dose of dabigatran before starting
	CrCl <30 mL/min	Wait 24 hrs after last dose of dabigatran before starting
Parenteral anticoagulant to dabigatran[b]	Start dabigatran 0-2 hours before the time the next dose of parenteral drug would be administered	
Heparin infusion to dabigatran	Start dabigatran when heparin infusion is discontinued	

a. Dabigatran can increase INR. INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days.
b. Parenteral anticoagulants: enoxaparin, fondaparinux, subcutaneous heparin, and heparin infusion.

Rivaroxaban (Xarelto®)

FDA Label Indications: See Dosing Table

Rivaroxaban Dosing		
Indication	**Dose**	**Dose Adjustment**
Non-valvular atrial fibrillation	20 mg PO daily with evening meal	CrCl 15-50 mL/min: 15 mg daily CrCl <15 mL/min: avoid use
Treatment of DVT or PE	15 mg PO BID X 21 days; then 20 mg PO daily thereafter. Taken with food.	CrCl <30 mL/min: avoid use
Knee replacement – post-op DVT prophylaxis	10 mg PO daily. Start at least 6-10 hrs after surgery and continue for 12 days without regard to food	CrCl <30 mL/min: avoid use
Hip replacement – post-op DVT prophylaxis	10 mg PO daily. Start at least 6-10 hrs after surgery and continue for 35 days without regard to food	CrCl <30 mL/min: avoid use
DVT/PE prophylaxis for risk of recurrent DVT/PE	20 mg PO daily x 6-12 months	CrCl <30 mL/min: avoid use

Note: discontinue in acute renal failure

Hepatic Adjustment:
Moderate or Severe (Child-Pugh B or C), or any hepatic disease associated with coagulopathy: avoid use.

Drug interactions:
Avoid use with combined P-gp and strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir.
Avoid use with combined P-gp and strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort.

Hold before surgery: At least 24 hours.
Epidural catheters should not be removed earlier than 18 hours after last rivaroxaban dose. The next rivaroxaban dose should not be given earlier than 6 hours after epidural catheter removal. If traumatic puncture occurs, rivaroxaban should not be given for 24 hours.

Monitoring:
During bleeds: PT and aPPT may be elevated in overdose.

Administration:
Give 15 mg and 20 mg tablet with food. The 10 mg tablets may be given with or without food.
Enteral tubes: May crush tablets, suspend in 50 mLs of water (stable x 4 hours), and give via enteral tubes that end in the stomach. Do not give via enteral tubes that end in the small intestine.

Missed Dose:
15 mg BID dose: take immediately to ensure intake of 30 mg per day. In this case, two 15 mg tablets can be taken together. Resume 15 mg dosing BID the following day.
Once daily dosing: take missed dose immediately.

Transitioning to or from Rivaroxaban	
Change	**Directions**
Rivaroxaban to warfarin[a]	Discontinue rivaroxaban and start parenteral anticoagulant and warfarin when the next rivaroxaban dose would have been given[b]
Warfarin to rivaroxaban	Discontinue warfarin, initiate rivaroxaban when INR < 3.0
Rivaroxaban to rapid onset anticoagulant[c]	Discontinue rivaroxaban and start first dose of other anticoagulant when next rivaroxaban dose would have been given
Non-warfarin anticoagulant to rivaroxaban[c]	Start rivaroxaban 0-2 hrs before next scheduled PM dose and omit administration of the other anticoagulant
Heparin infusion to rivaroxaban	Discontinue infusion and start rivaroxaban at the same time

a. Rivaroxaban affects INR. INR measurements during coadministration with warfarin may not be useful to determine the appropriate warfarin dose.
b. Parenteral anticoagulants: enoxaparin, fondaparinux, and subcutaneous heparin. General recommendation is to begin LMWH or UFH with warfarin until INR is clinically appropriate.
c. Enoxaparin, fondaparinux, subcutaneous heparin, apixaban, and dabigatran.