LOS ANGELES COUNTY DEPARTMENT OF HEALTH SERVICES
HARBOR-UCLA MEDICAL CENTER

SUBJECT: ANTICOAGULATION MANAGEMENT GUIDELINES **POLICY NO.** 325S

CATEGORY: Provision of Care	**EFFECTIVE DATE:** 6/19
POLICY CONTACT: Jennie Ung, PharmD	**UPDATE/REVISION DATE:** 1/22
REVIEWED BY COMMITTEE(S): Pharmacy and Therapeutics	

PURPOSE:
To provide evidence-based guidelines for the initiation and management of patients receiving anticoagulant therapy.

ABBREVIATIONS:

ACS = Acute coronary syndrome
ACT = Activated coagulation time
AF or AFib = Atrial fibrillation
APLS = Antiphospholipid syndrome
aPTT = Activated partial-thromboplastin time
BMI = Body mass index
CAD = Coronary artery disease
CBC = Complete blood count
CrCl = Creatinine clearance
CV = Cardiovascular
DOAC = Direct oral anticoagulant
DTI = Direct thrombin inhibitor
DVT = Deep venous thrombosis
ED = Emergency Department
eHR = electronic Health Record
HIT = Heparin-induced thrombocytopenia
HITT = Heparin-induced thrombocytopenia and thrombosis
INR = International Normalized Ratio
IV = Intravenous
LFT = Liver function test
LMWH = Low molecular weight heparin
MI = Myocardial infarction
NSTEMI = Non-ST-Elevation Myocardial Infarction
PAD = Peripheral artery disease
PCI = Percutaneous coronary intervention
PE = Pulmonary embolism
PT = Prothrombin time
RN = Registered Nurse
SQ = subcutaneous
tPA = Tissue Plasminogen Activator
UA = Unstable angina
UFH = Unfractionated heparin
VKA = Vitamin K antagonist
VTE = Venous thromboembolism

HUMC = Harbor UCLA Medical Center
NOTE—unless otherwise specified:
Anti-Xa = Anti-Xa, UFH (not the same as Anti-Xa for LMWH)
"Heparin" = unfractionated heparin

REVISED: 1/20, 1/22
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SUBJECT: ANTICOAGULATION MANAGEMENT GUIDELINES **POLICY NO.** 325S

BACKGROUND:
Anticoagulant medications inhibit the formation of blood clots. Therapeutic anticoagulation in adults is used in many clinical situations, the most common of which include:

- treatment and prevention of VTE disease,
- treatment of acute myocardial infarction,
- prevention of valve thrombosis and arterial thromboembolism in patients with artificial heart valves, and
- prevention of stroke in patients with atrial fibrillation.

Historically, most patients requiring parenteral anticoagulation received SQ LMWH or IV UFH. Those requiring oral anticoagulation received warfarin, a vitamin-K antagonist that has a narrow therapeutic index and requires frequent lab monitoring.

More recently, several non-vitamin K antagonist oral anticoagulants have been developed. These are alternately referred to as DOAC medications. Apixaban, betrixaban, edoxaban, and rivaroxaban inhibit factor Xa; dabigatran is a DTI.

Multidisciplinary coordination is necessary to maximize the benefits of anticoagulation while minimizing the risk of adverse events. This practice guideline aims to provide evidence-based clinical guidance for the management of therapeutic anticoagulation. It does not address prophylactic anticoagulation.

This guideline may not cover all indications or therapeutic options.

POLICY:
Providers, nurses, and other healthcare professionals at HUMC will follow the Anticoagulation Management Guidelines in the interest of patient safety.

PROCEDURE:

1. Provider selects anticoagulant therapy.
   Factors influencing the choice of anticoagulant medication include the site of care (e.g., inpatient vs outpatient), clinical indication, potential drug-drug interactions, and patient-specific factors (e.g., comorbidities, renal function, liver function, and patient preference). The following table is a general guide to the indications, advantages, and disadvantages of anticoagulant medications. It is intended to aid the provider in selection of an appropriate medication. Dosing and monitoring are addressed in subsequent sections. Dosing and monitoring can be found in the appendices or other relevant HUMC Hospital policies.

2. Provider discontinues all other prophylactic or therapeutic anticoagulants except argatroban, LMWH, or heparin bridging therapy for patients on warfarin.

3. Baseline and ongoing laboratory
   a. Baseline and ongoing laboratory tests must be ordered by provider prior to initiation of anticoagulant therapy, unless performed within 24 hours prior to initiation. Recommended baseline labs: PT/INR, aPTT, CBC, BUN/SCr, LFTs. Recommended ongoing labs: CBC, BUN/ SCr (periodically). Anti-Xa or other laboratory tests may be needed (see drug specific appendices or policies).
   b. Ongoing monitoring of bleeding risk and platelet count is recommended for all patients receiving anticoagulants.

4. Potential anticoagulant drug-drug and drug-food interactions must be reviewed prior to initiation of anticoagulant therapy (see drug-specific appendices or policies for potential interactions).
   a. The interaction lists provided are NOT inclusive of every possible drug-drug or drug-food interactions. The providers and/or RNs may contact the pharmacist to review potential interactions not listed in this policy.
   b. Most common potential drug-drug interactions—increases bleeding risk with concomitant use:
      i. Other anticoagulants (e.g., warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, heparin)
      ii. Drugs or herbs with antiplatelet properties (e.g., aspirin, clopidogrel, ibrutinib, limaprost, NSAIDs)
      iii. Thrombolytic agents: alteplase, streptokinase, urokinase, etc.

5. Patient education regarding anticoagulant therapy must be provided:
   a. During hospitalization: by provider or RN (**HUMC Policy 325Q**: Medication Administration).
   b. Upon discharge: Patients are provided medication-specific education on any anticoagulant that is initiated or changed at time of hospital discharge or in the outpatient setting (**HUMC Policy 335**: Outpatient Pharmacy).
   c. In addition to education provided to patients by providers/RNs, pharmacist will provide warfarin education to patients to emphasize on the importance of follow-up monitoring, compliance, drug-drug & drug-food interactions, and potential for adverse drug reactions.
   d. Outpatient setting: refer to outpatient anticoagulation policies

6. Quality assurance:
   The Pharmacy Department will perform periodic utilization review of anticoagulant and reversal agents, as well as protocol adherence to assess appropriateness.

Reviewed and approved by:
Medical Executive Committee - 01/2022

Beverley A. Petrie

Beverley A. Petrie, M.D.
President, Professional Staff Association

How to Select an Anticoagulant Medication

	Clinical Indications										Route	Considerations
	Arterial emboli	ACS	APLS	Bridging	Prosthetic valve	DVT/PE	HIT	Non-valvular AF	Valvular AF	PCI		
UFH ***HUMC Policy 371***	X	X	X	X	X	X		X	X	X	IV	- Narrow therapeutic window - Frequent monitoring required - Can be used with renal impairment - Can be used in pregnancy Risk of heparin-induced thrombocytopenia
LMWH ***Appendix A***		X	X	X	X	X		X	X	X	SQ	- Weight-based dosing - Caution with renal impairment - Can be used in pregnancy Effective for malignancy-associated VTE
Argatroban ***HUMC Policy 325P***							X				IV	- Can be used with renal impairment - Can be used for patients with history HIT and any other indication for anticoagulation
Bivalirudin ***Appendix B***										X	IV	- Use in conjunction with aspirin for patients undergoing PCI with (or at risk of) HIT/HITT
Fondaparinux ***Appendix C***		X		X		X					SQ	- Weight-based dosing - Cannot be used with CrCl < 30mL/min
Warfarin ***HUMC Policy 325T***	X		X		X	X		X	X		PO	- Many drug-drug and drug-food interactions - Narrow therapeutic window - Frequent lab monitoring required - Longer half-life - Can be used with renal impairment
Direct Oral Anticoagulant ***Appendix D*** (Dosing for adult patients) ***Appendix E*** (Rivaroxaban PA form)						X	X	X			PO	- Not for use in morbid obesity (BMI > 40 kg/m^2) - Not for use in pregnancy - Caution with renal or hepatic impairment - Avoid use with dual P-gp/CYP3A inhibitors and dual P-gp/CYP3A inducers

See ***Appendix F*** for transition of anticoagulants.
See ***Appendix G*** for guidelines for Anticoagulant Reversal for Adult Patients
See ***HUMC Policy 325U*** for Perioperative Management of Patients on Anticoagulants

Appendix A: Enoxaparin (Lovenox®) Dosing Guidelines

1. Use actual body weight for weight-based dosing.
2. Adult doses should be rounded to the nearest full syringe (see table **A1**)

Table A1: Enoxaparin dose rounding

Weight (kg)	How to round 1mg/kg/dose	Syringe size
< 100	Round to the nearest 10mg dose	60mg, 80mg, or 100mg
100-109	Round to 100mg	100mg
110-127	Round to 120mg	120mg
128-142	Round to 135mg	150mg
143-157	Round to 150mg	150mg
> 157	Round as appropriate with 2 syringes	2 syringes

3. See table **A4** for recommended prophylaxis dosing guidelines (adult patients).
4. See table **A5** for recommended treatment dosing guidelines (adult patients).
5. See table **A6** for recommended initial dosing guidelines (pediatric patients).
6. See table **A7** for recommended dose adjustment guidelines (adult patients).
7. See table **A8** for recommended dose adjustment guidelines (pediatric patients).
8. Preferred injection sites are the anterolateral or posterolateral abdominal wall. If abdominal access is limited, the upper outer quadrants of the thighs or buttocks can be used. Do not inject into the arms.
9. Monitoring guidelines:
   a. Routine anti-Xa monitoring is not recommended. It may be checked with long term therapy, labile/compromised renal function (CrCl < 30mL/min), pregnancy, or weight > 144kg. Peak anti-Xa should be drawn **4 hrs after 3rd or 4th dose** and after dosage modification—no more often than once weekly.
   b. See table **A2** below for recommended monitoring guidelines (adult patients):

Table A2: Enoxaparin Anti-Xa Monitoring Guidelines for Adult Patients

Enoxaparin	Anti-Xa, LMWH (units/mL)
Prophylactic dosing	0.2-0.5
Prophylactic dosing (pregnant women)	0.2-0.6
Therapeutic dosing (1 mg/kg q12h)	0.6-1
Therapeutic dosing (1.5 mg/kg q24h)	1-2

   c. See table **A3** below for recommended monitoring guidelines (pediatric patients):
      i. Patients weighing < 50kg (prophylaxis & treatment)
      ii. Patients weighing > 50kg with renal impairment (treatment):

Table A3: Enoxaparin Anti-Xa Monitoring Guidelines for Pediatric Patients

Indication	Target Anti-Xa, LMWH (unit/mL)
Prophylaxis	0.1-0.3
Treatment	0.5-1.0

10. Contraindications:
    a. Active major bleeding

b. Thrombocytopenia with a positive test of antiplatelet antibody
c. History of HIT with UFH or LMWH
d. Hypersensitivity to heparin or pork and/or beef products

11. Contact anticoagulant specialist (page (310) 501-9865)) for:
    a. Use in patients with body weight >190 kg (or 420 lb) or <45 kg (or 100 lb)
    b. LMWH therapy planned for >30 days
12. Increased risk of bleeding complications is associated with neuraxial intervention (e.g., epidural catheters, lumbar puncture or surgery).
    a. Delay placement or removal of catheter for at least 12 hrs after administration of low-dose enoxaparin (e.g., 30-60mg/day) and at least 24 hrs after high-dose enoxaparin (0.75-1mg/kg twice daily or 1.5mg/kg once daily) and consider doubling these times in patients with CrCl < 30mL/min.
    b. Upon removal of catheter, consider withholding enoxaparin for at least 4 hrs.

Table A4: Enoxaparin Prophylaxis Dosing Guidelines for Adult Patients

PROPHYLAXIS	ENOXAPARIN		Typical Duration
	Dosage (CrCl ≥ 30mL/min)	Dosage (CrCl <30 mL/min)	
Trauma, Orthopedic or acute spinal cord injury	30mg SQ q12h	30mg SQ q24h	7-10 days
High or Very High Risk Medical patients	40mg SQ q24h	30mg SQ q24h	6-11 days
Morbid obesity (BMI ≥ 40 kg/m^2)	40mg SQ q12h or Increase standard dose by 30%	No recommendation	Variable
High VTE-risk bariatric surgery (BMI ≤ 50 kg/m^2)*	40mg SQ q12h	No recommendation	Variable
High VTE-risk bariatric (BMI >50 kg/m^2)*	60mg SQ q12h	No recommendation	Variable
Abdominal surgery	40mg SQ q24h (2h prior to surgery)	No recommendation	7-10 days
Hip replacement surgery	*Once-daily dosing:* 40mg SQ x1 (9-15h pre-op) & 40mg SQ q24h (≥ 12h post-surgery) *Twice-daily dosing:* 30mg SQ x1 (≥12 hours pre-op) & 30mg SQ q12h (12-24h post-surgery)	30mg SQ (≥12 hours pre-op) & 30mg SQ q24h (≥ 12h post-surgery)	At least 10 days (up to 35 days) or until risk of DVT has diminished or until target INR is achieved with warfarin
Knee replacement surgery	30mg SQ x1 (≥12 hours pre-op) & 30mg SQ q12h (12-24h post-surgery)	30mg SQ q24h	
Prevention of recurrent VTE in pregnancy (*off-label*)	40mg SQ q24h	No recommendation	6 weeks postpartum in high-risk women

Table A5: Enoxaparin Treatment Dosing Guidelines for Adult Patients

TREATMENT	ENOXAPARIN		Typical Duration
	Dosage (CrCl ≥ 30mL/min)	Dosage (CrCl <30 mL/min)	
Suspected/confirmed acute DVT/PE† Peri-procedure bridging	1 mg/kg SQ q12h	1 mg/kg SQ q24h†	5-7 days or until target INR (2-3) is achieved on 2 consecutive days with warfarin

Acute VTE in obesity	- Use actual body weight - Dose capping NOT recommended - Twice-daily dosing preferred	No recommendation	
Acute VTE in pregnancy *(off-label)*	1 mg/kg SQ q12h	No recommendation	Discontinue ≥ 24h prior to induction of labor or C-section; Substitute enoxaparin with heparin near term. Continue anticoagulation therapy for ≥ 6 wks postpartum (minimum total duration of 3 months)
Acute STEMI* w/thrombolytic treatment	AGE <75 years 30 mg IVP x1, PLUS 1mg/kg SQ q12h x2 doses (max 100mg for the first 2 doses), then 1mg/kg SQ q12h	AGE <75 years 30mg IVP x1, PLUS 1mg/kg SQ q24h	48-72 hours (maybe initiated 15 minutes before and 30 minutes after initiating thrombolytic therapy)
	AGE ≥ 75 years 0.75mg/kg SQ q12h x2 doses (max 75mg for the first 2 doses), then 0.75mg/kg SQ q12h	AGE ≥ 75 years 1mg/kg SQ q24h	48-72 hours
NSTEMI/Unstable Angina	1 mg/kg SQ q12h	1mg/kg SQ q24h	48-72 hours

†Heparin is preferred over LMWH in patients with impaired renal function (CrCl <30 ml/min). Enoxaparin may be used at renally-adjusted doses for short term transition to warfarin.
*For treatment of STEMI, enoxaparin may be initiated 15 minutes before and 30 minutes after initiating thrombolytic therapy. Therapy may be continued for 8 days and a minimum of 48 hours in patients undergoing reperfusion with thrombolytic therapy.

Table A6: Enoxaparin Initial Dosing Guidelines for Pediatric Patients

Indication	< 5kg	5-50kg	> 50kg	
Prophylaxis	0.75mg/kg/dose SQ q12h = _____mg SQ q12h	0.5mg/kg/dose SQ q12h = _____mg SQ q12h (NOT to exceed 40mg/day)	CrCl ≥ 30 mL/min 40mg SQ q24h	CrCl < 30 mL/min 30mg SQ q24h
Treatment	1.5mg/kg/dose SQ q12h = _____mg SQ q12h	1mg/kg/dose SQ q12h = _____mg SQ q12h	1 mg/kg SQ q12h	1 mg/kg SQ q24h

Table A7: Enoxaparin Dose Adjustment Guidelines for Adult Patients

Peak anti-Xa (unit/mL)	Recommended Dosage Adjustment for therapeutic q12h dosing
< 0.35	Increase dose by 25%
0.35-0.49	Increase dose by 10%
0.5-1.0	None
1.1-1.5	Decrease dose by 20%
1.6-2	Delay next dose by 3 hours& Decrease dose by 30%
>2	Delay next dose until anti-Xa level < 0.5 & Decrease dose by 40%

Table A8: Enoxaparin Dose Adjustment Guidelines for Pediatric Patients*

4-hr peak anti-Xa (unit/mL)	Hold next dose?	Dose Change	Obtain Repeat anti-Xa levels
< 0.35	No	Increased by 25%	Next day
0.35-0.49	No	Increased by 10%	Next day
0.5-1.0	No	No change	Next week
1.1-1.5	No	Decreased by 20%	Next day
1.6-2	X 3hrs	Decreased by 30%	Before next dose AND next day
>2	All further doses should be held and anti-Xa levels measured q12h until < 0.5unit/mL. Decrease previous dose by 40% when restarted.		

**nomogram to be used for treatment dosing*

Appendix B: Bivalirudin (Angiomax®) Dosing Guidelines for Adult Patients

Note: Bivalirudin is restricted to Cardiology.

1. Anti-Xa activity for fondaparinux is not available at HUMC.
2. See table **B1** for recommended dosing guidelines.
3. Contraindication:
    a. Active major bleeding
    b. Severe hypersensitivity to bivalirudin or any component of the formulation
4. No dosage adjustment necessary for hepatic impairment.
5. PT/INR levels may become elevated in the absence of warfarin.
6. If clinically indicated, provisional glycoprotein (GP) IIb/IIIa inhibition (e.g., eptifibatide) may be concomitantly administered during PCI. In addition to aspirin, concomitant administration of clopidogrel, or prasugrel, is also recommended for patients undergoing PCI.

Table B1: Bivalirudin Dosing Guidelines for Adult Patients

Indication	Dosage
PTCA/PCI with or without HIT	**Initial**: 0.75mg/kg bolus immediately prior to procedure, then 1.75mg/kg/hr for the duration of procedure and up to 4 hrs post procedure if needed. **After initial 4-hr post procedure**: 0.2mg/kg/hr for up to additional 20 hours Monitor ACT 5 minutes after bolus dose & may administer additional bolus 0.3mg/kg if necessary.
UA/NSTEMI (moderate-high risk) undergoing early invasive strategy	**During PCI:** 0.75mg/kg bolus immediately prior to procedure, then 1.75mg/kg/hr
STEMI (U.S. off-label)	**Initial**: 0.75mg/kg bolus immediately prior to procedure, then 1.75mg/kg/hr for the duration of procedure and up to 4 hrs post procedure if needed. May continue post procedure at a reduced dose if clinically indicated. For patients with high risk of bleeding, it is reasonable to use bivalirudin monotherapy.

Appendix C: Fondaparinux (Arixtra®) Dosing Guidelines for Adult Patients

Note: Fondaparinux is restricted to orthopedics or patients requiring anticoagulation that have suspected acute Heparin-Induced-Thrombocytopenia (HIT) or a confirmed history of HIT.

1. Anti-Xa activity for fondaparinux is not available at HUMC.
2. See table **C1** for recommended dosing guidelines.
3. Contraindication:
    a. Severe renal impairment (CrCl < 30mL/min)
    b. Body weight < 50kg for VTE prophylaxis
    c. Active major bleeding

d. Bacterial endocarditis
e. Severe hypersensitivity to fondaparinux or any component of the formulation
f. Thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of fondaparinux

4. Increased risk of bleeding complications are associated with neuraxial intervention (e.g., epidural catheters, lumbar puncture or surgery). Optimum timing between administration of fondaparinux and neuraxial procedures is unknown.

Table C1: Fondaparinux Dosing Guidelines for Adult Patients

	PROPHYLAXIS	TREATMENT for acute VTE		
CrCl (mL/min)	**Weight > 50kg**	**<50kg**	**50-100kg**	**>100kg**
> 50	2.5mg SQ q24h	5mg SQ q24h	7.5mg SQ q24h	10mg SQ q24h
30-50	2.5mg SQ q48h	2.5mg SQ q24h	5mg SQ q24h	7.5mg q24h
< 30	**CONTRAINDICATED**			

Appendix D: Direct Oral Anticoagulant Dosing Guidelines for Adult Patients

*NOTE: current DOAC on DHS formulary is rivaroxaban (10, 15, & 20mg)—(*see **appendix E** for *Rivaroxaban Prior Authorization Form).*

1. DOACs differ from vitamin K antagonists in their onset of action, half-life, drug-drug interactions, need for monitoring, and availability of antidotes.
2. DOACs are generally used without a requirement for monitoring of drug levels or coagulation times; this may be an advantage for patients in whom frequent monitoring is a greater burden.
3. Patients with difficulty in controlling PT/INR may benefit from a DOAC because these agents have less variability in drug effect than vitamin K antagonists.
4. See table **D1** for recommended dosing guidelines for rivaroxaban.
5. See table **D2** for recommended dosing guidelines for the other DOACs ***NOT*** currently on DHS formulary.
6. See table **D3** for common drug-drug interactions with DOACs and recommended dosage adjustments.
7. A therapeutic anti-Xa range for DOAC has NOT been defined.
8. PT or anti-Xa activity may be used to detect presence of DOAC, but neither can be used for dose adjustment.
9. Contraindications:
   a. Active major bleeding
   b. Severe hypersensitivity to any component of the formulation
10. Bleeding risk is increased when DOACs are combined with ADP antagonists, such as clopidogrel. Consultation with a cardiologist is recommended in this situation.
11. Risk of bleeding complications increased with neuraxial intervention (e.g., epidural catheters, lumbar puncture or surgery).
    c. Apixaban:
       - Delay placement or removal of catheter for at least 24 hours after the last administration of apixaban.
       - Upon removal of catheter, consider withholding apixaban for at least 5 hours.
       - If traumatic puncture occurs, delay the administration of apixaban for 48 hours.
    d. Betrixaban:

- Delay placement or removal of catheter for at least 72 hours after the last administration of betrixaban.
- Upon removal of catheter, consider withholding betrixaban for at least 5 hours.
- If traumatic puncture occurs, delay the administration of betrixaban for 72 hours.

e. Edoxaban:
- Delay placement or removal of catheter for at least 12 hours after the last administration of edoxaban.
- Upon removal of catheter, consider withholding edoxaban for at least 2 hours.
- If traumatic puncture occurs, the risk may increase.

f. Rivaroxaban:
- Delay placement or removal of catheter for at least 2 half-lives after the last administration of rivaroxaban (i.e., 18 hours in patients aged 20-45 years and 26 hours in patients aged 60-76 years).
- Upon removal of catheter, consider withholding rivaroxaban for at least 6 hours.
- If traumatic puncture occurs, delay the administration of rivaroxaban for 24 hours.

g. Dabigatran: Optimum timing between administration of dabigatran and neuraxial procedures is unknown.

Table D1: Recommended Dosing Guidelines for Rivaroxaban (adult patients)

Indication	Dosage
To reduce risk of stroke & systemic embolism in patients with non-valvular AF	CrCl ≥ 50mL/min: 20mg daily with evening meal **OR** 15mg daily with evening meal (if combined with clopidogrel) CrCl < 50mL/min: 15mg daily with evening meal
Acute VTE treatment (CrCl > 30mL/min)	CrCl ≥ 15mL/min: 15mg BID with food for 21 days, followed by 20mg daily with food for remaining treatment CrCl < 15: Not recommended
To reduce risk of recurrence DVT/PE in patients at continued risk for recurrent DVT/PE (after completion of initial treatment lasting at least 6 months of standard anticoagulant)	CrCl ≥ 15mL/min: 20mg daily with food **OR** 10mg daily (EINSTEIN CHOICE trial) CrCl < 15: Not recommended
DVT/PE prophylaxis (total knee arthroplasty)	CrCl ≥ 15mL/min: 10mg daily for 12-14 days (initial dose 6-10 hrs after surgery once hemostasis established) CrCl < 15: Not recommended
DVT/PE prophylaxis (hip arthroplasty)	CrCl ≥ 15mL/min: 10mg daily for 35 days (initial dose 6-10 hrs after surgery once hemostasis established) CrCl < 15: Not recommended
*In combination of aspirin, to reduce risk of major cardiovascular events (CV, MI, and stroke) in patients with CAD or PAD	*2.5mg twice daily with or without food, in combination with aspirin 75mg to 100mg daily

Table D2: Recommended Dosing Guidelines for DOACs *NOT* currently on DHS formulary (adult patients)

FDA approved indications	Direct Factor Xa Inhibitors			Direct Thrombin Inhibitor
	Apixaban (Eliquis®)	Edoxaban (Savaysa®)	Bevyxxa (Betrixaban®)	Dabigatran (Pradaxa®)
Non-valvular atrial fibrillation (NVAF)	• 5mg BID • 2.5mg BID with any 2 of the following: age ≥ 80 years, weight ≤ 60kg or SCr ≥ 1.5 mg/dL •	• CrCl > 95mL/min: NOT recommended (drug may be cleared too rapidly) • CrCl 51-95mL/min: 60mg daily • CrCl 15-50mL/min: 30mg daily • CrCl < 15mL/min: not recommended	Not approved	• CrCl > 30mL/min: 150mg BID • CrCl 15-30mL/min: 75mg BID • CrCl < 15mL/min: not recommended • CrCl 30-50mL/min **with** dronedarone or PO ketoconazole: 75mg BID
Acute VTE treatment (LMWH and edoxaban preferred in patients with active cancer)	• CrCl ≥ 15mL/min: 10mg BID for 7 days, then 5mg BID • CrCl < 15: No clinical studies	• Begin after 5-10 days of initial therapy with a parenteral anticoagulant • CrCl > 51mL/min: 60mg daily • CrCl 15-50mL/min or weight ≤ 60kg or on P-gp inhibitor: 30mg daily • CrCl < 15ml/min: not recommended	Not FDA approved	• For VTE treatment, an initial 5-10 days of parenteral anticoagulation is required before initiating dabigatran • CrCl > 30mL/min: 150mg BID • CrCl ≤ 30mL/min: not recommended
VTE secondary prevention	• CrCl ≥ 15mL/min: 5mg BID May consider 2.5mg BID per AMPLIFY-EXTEND trial • CrCl < 15: No clinical studies	Not approved	Not FDA approved	• CrCl > 30mL/min: 150mg BID • CrCl ≤ 30mL/min: not recommended
Post-Op VTE prophylaxis	• Start 12-24 hours post-op • Total hip arthroplasty: 2.5mg BID for 25 days • Total knee arthroplasty: 2.5mg BID for 12 days • CrCl <30mL/min: no clinical studies	Not approved	• CrCl ≥30mL/min: 160mg x1 on day 1, followed by 80mg daily x 35-42 days • CrCl 15-30mL/min: 80mg x1 on day 1, followed by 40mg daily x 35-42 days	• Start 1-4 hours post-op • CrCl >30mL/min: 110mg x1, then 220mg daily • Duration: - 10-14 days for total knee arthroplasty - 28-35 days for total hip arthroplasty • CrCl ≤30mL/min or on dialysis: dosing recommendations not available • CrCl <50mL/min w/ concomitant use of P-gp inhibitors: avoid co-administration

Table D3: Common Drug-Drug Interactions with DOACs & Recommended Dosage Adjustments (adult patients)

Direct Factor Xa Inhibitors				Direct Thrombin Inhibitor
Rivaroxaban (Xarelto)	**Apixaban (Eliquis)**	**Edoxaban (Savaysa)**	**Betrixaban (Bevyxxa)**	**Dabigatran (Pradaxa)**
Do not use in combination with: -Dual P-gp and strong CYP3A4 inhibitors* -Dual P-gp and strong CYP3A4 inducers* **Avoid use with** dual P-gp and moderate CYP3A4 inducers if CrCl < 80mL/min **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, NSAID, SSRI, and SNRI medications	**Dual P-gp and strong CYP3A4 Inhibitors** -Doses >2.5mg BID: reduce dose by 50% -2.5mg BID: avoid use **Dual P-gp and strong CYP3A4 Inducers** -Avoid use **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, NSAID, SSRI, and SNRI medications	**P-gp Inhibitors** -NVAF: no dose reduction recommended -VTE treatment: 30mg PO once daily **P-gp Inducers** -Avoid use **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, and NSAID medications	**P-gp Inhibitors** • CrCl ≥ 30mL/min: Reduce dose (initial and maintenance) by 50% • CrCl < 30mL/min: avoid use	**P-gp Inhibitors** • NVAF+CrCl 30-50mL/min: consider dabigatran 75mg BID • NVAF+CrCl 15-30mL/min: avoid • VTE+CrCl < 50mL/min: avoid • Can lead to increased exposure to dabigatran and risk of bleeding **P-gp Inducers** • Avoid use • Can lead to reduced exposure to dabigatran and may decrease efficacy **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI** • May increase bleeding risk

P-gp = p-glycoprotein, NSAID = non steroidal anti-inflammatory drug, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor, CYP3A4 = cytochrome P450 3A4, NVAF = non valvular atrial fibrillation

- Examples of P-glycoprotein & CYP3A4 inhibitors/inducers. Consult references such as Micromedex or Lexi-Comp for complete drug interaction information.
- Examples of inducers:
  - P-glycoprotein inducer: carbamazepine, rifampin, St John's wort
  - CYP3A4 inducer: carbamazepine, phenobarbital, phenytoin, pioglitazone, rifampin, rifabutin, St John's wort
- Examples of inhibitors:
  - P-glycoprotein inhibitor: amiodarone, itraconazole, ketoconazole, macrolides, quinidine, ritonavir, verapamil
  - CYP3A4 inhibitor: amiodarone, azoles, diltiazem, isoniazid, macrolides, quinolones, ritonavir, valproic acid

Appendix E: Rivaroxaban Prior Authorization Form

Rivaroxaban (Xarelto®) Prior Authorization Form

Health Services

Instructions

1. Please complete all sections of the form. Incomplete forms will be returned to the prescriber.
2. Submit form along with the prescription order to the facility pharmacy. This form is not a substitute for a prescription order. Any form submitted without a prescription order will be considered incomplete and not reviewed.
3. Inpatient/Outpatient use: CMO or designee approval is not needed for cases where the criteria are met. If all criteria below are not met, form will be forwarded by the facility pharmacy to DHS Pharmacy Affairs for review. The CMO or designee will provide final decision in these cases.

Notes

1. This prior authorization form must be submitted for all written inpatient or outpatient prescriptions.
2. Authorizations are limited to a maximum of twelve (12) months of therapy. Additional authorization is required for any use after this initial 12-month period.
3. Please complete ALL areas below. An incomplete prior authorization request MAY AFFECT THE OUTCOME of this request.

STEP 1: EXCLUSION CRITERIA *(if any of the following criteria apply, the patient does NOT qualify for rivaroxaban use). Check box in Step 1 below to acknowledge.*

Prosthetic heart valve	Patient has known hypersensitivity to rivaroxaban
Clinically significant valvular disease (e.g., moderate to severe mitral valve stenosis)	Patient had a stroke within 14 days, a severe disabling stroke within the previous 3 months, or a TIA within the past 3 days
Patient has a CrCl less than 15mL/min in atrial fibrillation (or less than 30mL/min for VTE prophylaxis and treatment)	Patient has known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis, liver function test [LFT] elevations greater than 3x upper limit of normal, Child-Pugh class B or C)
Patient is pregnant or breastfeeding	Concomitant therapy with P-glycoprotein (P-gp) and/or strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, and simeprevir)
Patient has active endocarditis	Concomitant therapy with combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort)
Patient has undergone epidural or spinal anesthesia within the last 24 hours	Patient has a history of, or condition associated with, increased bleeding risk (e.g., active pathological bleeding, major surgery or trauma within the previous month, gastrointestinal bleed within the past 6 months, history of intracranial, intraocular spinal, retroperitoneal or atrioventricular intracranial bleeding, intracranial neoplasm, arteriovenous malformation, aneurysm, or chronic hemorrhagic disorder)
☐ Patient has NONE of the exclusion criteria listed above	

STEP 2: APPROVAL CRITERIA *(Check appropriate indication below, then Check ALL associated criteria that apply. Note: Any incomplete information MAY AFFECT THE OUTCOME of this request.*

☐ Atrial Fibrillation Stroke Prevention	☐ Orthopedic Surgery VTE Prophylaxis
☐ • Diagnosis of non-valvular atrial fibrillation (documented by electrocardiogram and echocardiogram) • Patient has a CHADS2 or CHA2DS2-VASc score greater than equal to 1, or prior TIA, stroke or systemic embolism. • Patient has a CrCl greater than equal to 15mL/min, patient's current CrCl: _____ mL/min	☐ Patient is indicated for VTE prophylaxis following total hip or total knee arthroplasty ☐ Patient has a CrCl greater than equal to 30mL/min, patient's current CrCl: _____ mL/min
AND ☐ Patient is not a candidate or is poorly controlled on warfarin therapy (e.g., history of INR >5 requiring intervention or hospitalization, history of bleeding event with supratherapeutic INR >5 while on warfarin, history of ≥2 subtherapeutic INR values <2.0 in prior 6 months, difficulty achieving/maintaining therapeutic INR requiring frequent clinic visits, allergy or intolerance to warfarin, documented non-adherence issues)	☐ Deep Vein Thrombosis, Pulmonary Embolism Treatment
OR ☐ Patient has planned cardioversion within next 6 weeks (treatment duration of 6 weeks prior to cardioversion and 4 weeks after cardioversion)	☐ Patient has objectively confirmed VTE (DVT and/or PE) ☐ Patient has a CrCl greater than equal to 30mL/min, patient's current CrCl: _____ mL/min ☐ Patient does NOT have VTE in the setting of active cancer

STEP 3: DOSAGE *(Check the appropriate dosage)*

☐ 20mg once daily with evening meal for AFib patients with CrCl greater than 50mL/min	☐ 10mg once daily for 12-14 days in total knee arthroplasty, therapy to initiated at least 6-10 hours after surgery once hemostasis is established
☐ 15mg once daily with evening meal for AFib patients with CrCl of 15-50mL/min	☐ 10mg once daily for 35 days in total hip arthroplasty, therapy to initiated at least 6-10 hours after surgery once hemostasis is established
☐ 15mg twice daily with food for 21 days, followed by 20mg daily with evening meal for patients with CrCl greater than equal to 30mL/min in acute VTE setting	☐ Other _____ (Specify dose and frequency; explain below)

STEP 4: ADDITIONAL EXPLANATION *(For additional comments, please attach to form)*

STEP 5: PRESCRIBER INFORMATION

Prescriber Name (Printed):		Prescriber Signature
Prescriber ID #:	Clinic/Ward:	
Telephone/Pager #:	Date:	*I declare that the information on this form, to my best knowledge and belief, is true, correct, and complete*

STEP 6: ATTACH TO ORIGINAL PRESCRIPTION

Pharmacy Review: Approval criteria met? ☐ YES ☐ NO If not met, submit to CMO or designee		
Date Received:	Date of Decision:	
Pharmacist Reviewer:		
Medical Review: ☐ Approved ☐ Denied		
Date Received:	Date of Decision:	
CMO or Designee:		

Appendix F: Transition between anticoagulant agents:

Table F1: Transition between parenteral anticoagulants

From	To	Instructions:
Argatroban	**Other parenteral anticoagulant** (argatroban, fondaparinux, LMWH, IV UFH*) *Use LMWH or UFH only if patient does NOT have heparin allergy or HIT.*	• If no hepatic insufficiency, start parenteral anticoagulant within 2 hrs of discontinuing argatroban infusion. • If hepatic insufficiency, start parenteral anticoagulant 2-4 hrs of discontinuing argatroban infusion.
Fondaparinux (therapeutic)		Start parenteral anticoagulant at time of next scheduled dose of fondaparinux.
Fondaparinux (prophylaxis)		Start parenteral anticoagulant as clinically needed irrespective of time of last fondaparinux dose.
LMWH (therapeutic)		• Start parenteral anticoagulant at time of next scheduled dose of LMWH. • No UFH bolus needed if UFH is scheduled to start 4-6hrs after the last dose of LMWH
LMWH (prophylaxis)		Start parenteral anticoagulant as clinically needed irrespective of time of last LMWH dose.
UFH		Start parenteral anticoagulant within 2 hrs of discontinuing UFH infusion.

**In case of high bleeding risk, consider omitting initial bolus when transitioning to UFH.*

Table F2: Transition from DOAC agents to other rapid-onset anticoagulants**

From	To	Instructions:
Rivaroxaban	**Rapid-onset anticoagulant** (LMWH, fondaparinux, DOACs or IV UFH*)	• Stop rivaroxaban. • Start other anticoagulant at time of next scheduled dose of rivaroxaban.
Apixaban		• Stop apixaban. • Wait 12 hours after last dose of apixaban to initiate other anticoagulant.
Edoxaban		• Stop edoxaban. • Start other anticoagulant at time of next scheduled dose of edoxaban.
Dabigatran		• Stop dabigatran. • Start other anticoagulant at time of next scheduled dose of dabigatran. • If CrCl < 15mL/min while on dabigatran, longer wash out period may be needed before starting new anticoagulant.

**In case of high bleeding risk, consider omitting initial bolus when transitioning to UFH.*
***Betrixaban and rivaroxaban (doses ≤ 10mg/day) to all other anticoagulants: initiate other anticoagulant as clinically needed irrespective of time of last betrixaban or rivaroxaban dose.*

Table F3: Transition from warfarin to DOACs

From	To	Instructions:
Warfarin	**Rivaroxaban**	Stop warfarin. Start rivaroxaban when INR is < 3.0
	Apixaban	Stop warfarin. Start apixaban when INR is < 2.0
	Betrixaban	Stop warfarin. Start edoxaban when the INR is ≤ 2.2
	Edoxaban	Stop warfarin. Start edoxaban when the INR is ≤ 2.5
	Dabigatran	Stop warfarin. Start dabigatran when INR is < 2.0

Table F4: Transition from DOAC agents to warfarin

	Transition to warfarin
Rivaroxaban (doses ≥ 15mg/day) to warfarin	• No clinical trial data available • Rivaroxaban affects INR, so INR measurements during co-administration with warfarin may not reflect the appropriate dose of warfarin **Transition Options** • Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken (XARELTO package insert information)[i] • Overlap rivaroxaban and VKA therapy until the INR is within the therapeutic range (ASH 2018 guidelines)[ii]
Apixaban to warfarin	• Apixaban affects INR, so INR measurements during co-administration with warfarin may not reflect the appropriate dose of warfarin **Transition Options** • Discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken (ELIQUIS package insert information)[iii] • Overlap apixaban and VKA therapy until the INR is within the therapeutic range (ASH 2018 guidelines)
Edoxaban to warfarin	**Transition Options**[iv] • Oral option: - For patients taking 60 mg edoxaban, reduce dose to 30 mg and begin warfarin concomitantly - For patients taking 30 mg edoxaban, reduce dose to 15 mg and begin warfarin concomitantly - Once a stable INR ≥ 2.0 is achieved, discontinue edoxaban and continue warfarin (INR should be measured just prior to daily dose of edoxaban to minimize influence of edoxaban on INR) • Parenteral option: - Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose - Once stable INR ≥ 2 is achieved, discontinue parenteral anticoagulant & continue warfarin
Dabigatran[v] to warfarin	• Dabigatran may affect INR. INR reflects warfarin's effect best after dabigatran has been stopped for at least 2 days

CrCl (mL/min)	Instructions:
CrCl ≥ 50	Start warfarin 3 days before discontinuing dabigatran
CrCl 30-50	Start warfarin 2 days before discontinuing dabigatran
CrCl 15-30	Start warfarin 1 day before discontinuing dabigatran
CrCl < 15	No recommendations available

Table F5: Transition from parenteral anticoagulants to oral anticoagulants

From	To	Instructions:
Argatroban	**DOACs**	Stop IV argatroban. Start a DOAC within 2 hours after discontinuation of argatroban.
	Warfarin	• Argatroban must be continued when warfarin is initiated and co-administration should continue for at least 5 days. Argatroban falsely elevates INR. • After 3-5 days of co-therapy with warfarin, if INR > 4, temporarily suspend argatroban for 4 hours, then check INR. - If INR < 2, restart argatroban & consider warfarin dose adjustment. Repeat process q24-48h until INR ≥ 2.0. - If INR ≥ 2.0 ***and*** overlap argatroban/warfarin for at least 5 days, discontinue argatroban and continue warfarin. - If INR > 3, consider warfarin dose adjustment. Argatroban may need to be restarted if argatroban/warfarin overlap has not been prescribed for 5 days.
Fondaparinux (therapeutic)	**DOACs**	Stop fondaparinux. Start a DOAC at time of next scheduled dose of fondaparinux.
	Warfarin	Begin warfarin when clinically indicated. Overlap fondaparinux with warfarin for at least 5 days **and** until INR is therapeutic for 24 hours if indicated
Fondaparinux (prophylaxis)	**DOACs**	Initiate a DOAC as clinically indicated irrespective of time of last fondaparinux dose.
	Warfarin	Assuming patient does NOT have a new thrombosis: if immediate therapeutic anticoagulation is not desired, initiate warfarin as clinically needed irrespective of time of last fondaparinux dose.
LMWH (therapeutic)	**Rivaroxaban**	Stop LMWH. Start rivaroxaban 0-2 hours before the time of the next scheduled evening dose of LMWH.
	Apixaban	Stop LMWH. Start apixaban at time of next scheduled dose of LMWH.
	Edoxaban	Stop LMWH. Start edoxaban at time of next scheduled dose of LMWH.
	Dabigatran	Stop LMWH. Start dabigatran 0-2 hours before the time of next scheduled dose of LMWH.
	Warfarin	Begin warfarin when clinically indicated. Overlap LMWH with warfarin for at least 5 days **and** until INR is therapeutic for 24 hours if indicated
LMWH (prophylaxis)	**DOACs**	Initiate a DOAC as clinically indicated irrespective of time of last LMWH dose.
	Warfarin	Assuming patient does NOT have a new thrombosis: if immediate therapeutic anticoagulation is not desired, initiate warfarin as clinically needed irrespective of time of last LMWH dose.
UFH	**DOACs**	Stop IV UFH. Start a DOAC immediately after discontinuation of UFH.
	Warfarin	Begin warfarin when clinically indicated. **If immediate therapeutic anticoagulation is desired**: Overlap therapeutic UFH with warfarin for at least 5 days **and** until INR is therapeutic for 24 hours **If immediate therapeutic anticoagulation is NOT desired**: initiate warfarin as clinically needed irrespective of time of last UFH dose.

Appendix G: Guidelines for Anticoagulant Reversal for Adult Patients

- Attending physician approval is required for andexanet alfa (Andexxa®) and 4-factor PCC (Kcentra®)—Attending of service may approve the first dose.
- Prior Authorization form must be completed for andexanet alfa and Kcentra® (see **F1 and F2 or Micromedex Formulary Tool**)
- For subsequent doses or additional questions, consider Hematology consult (pager (310) 501-9865).

<table>
<tr><th>Class</th><th>Anticoagulant</th><th>Half-life</th><th>Removed by HD</th><th>Strategies to reverse or minimize anticoagulant effects</th></tr>
<tr><td rowspan="4">Factor Xa Inhibitor</td><td>Apixaban (Eliquis®)</td><td>8-15 hrs (longer in renal impairment)</td><td>No</td><td rowspan="2">• General measure: stop DOAC & antiplatelet medications & provide volume support/transfusion
• If ingested within 2 hours, administer activated charcoal 100g
• 4-factor PCC (Kcentra®)
- 25units/kg—max 2500 units for treatment of documented intracranial hemorrhage
- 50 units/kg—max 5000 units for all other life-threatening bleeds
• Andexanet Alfa – see chart for dosing
<table><tr><th colspan="2"></th><th>Timing of last dose (rivaroxaban or apixaban)</th></tr><tr><th colspan="2"></th><th>Last dose < 8 hrs ago or unknown</th><th>Last dose ≥ 8 hrs ago</th></tr><tr><td rowspan="2">Strength of last</td><td>Rivaroxaban > 10mg
OR
Apixaban > 5mg
OR
Unknown dose</td><td>High dose andexanet alfa:
• Initial IV bolus: 800mg at 30mg/min
• Follow-On IV infusion: 8mg/min (up to 120 min)</td><td>Low dose andexanet alfa:
• Initial IV bolus: 400mg at 30mg/min
Follow-On IV infusion: 4mg/min (up to 120 min)</td></tr><tr><td>Rivaroxaban ≤ 10mg
OR
Apixaban ≤ 5mg</td><td colspan="2">Low dose andexanet alfa:
• Initial IV bolus: 400mg at 30mg/min
• Follow-On IV infusion: 4mg/min for up to 120 min</td></tr></table></td></tr>
<tr><td>Rivaroxaban (Xarelto®)</td><td>9-13 hrs (longer in renal impairment)</td><td>No</td></tr>
<tr><td>Edoxaban (Savaysa®)</td><td>10-14 hrs (longer in renal impairment)</td><td>~ 25%</td><td rowspan="2">• No known reversal agent or specific antidote, consider off-label treatment with:
• If ingested within 2 hours, administer activated charcoal 100g
• 4-factor PCC (KCentra®)
- 25units/kg—max 2500 units for treatment of documented intracranial hemorrhage
- 50 units/kg—max 5000 units for all other life-threatening bleeds</td></tr>
<tr><td>Betrixaban (Bevyxxa®)</td><td>19-27 hrs</td><td>Unknown</td></tr>
</table>

	Fondaparinux (Arixtra®)	17-21 hrs (significantly longer in renal impairment)	No	• 4-factor PCC (Kcentra®) 50 units/kg—max 5000 units
Direct Thrombin Inhibitor	Argatroban	40-50 min	~ 20%	• Turn off infusion
	Bivalirudin (Angiomax®)	25 min (up to 1hr in severe renal impairment)	~ 25%	
	Dabigatran (Pradaxa®)	14-17 hrs (up to 34 hrs in severe renal impairment)	~ 65%	• If ingested within 2 hours, administer activated charcoal 100g • Idarucizumab (Praxbind®) 5g IV • For end stage renal disease patient with pre-existing vascular access, consult nephrology to consider dialysis.

<table>
<tr>
<td>Low Molecular Weight Heparin</td>
<td>Dalteparin (Fragmin®)
Enoxaparin (Lovenox®)</td>
<td>3-5 hrs (longer in renal impairment)</td>
<td>~ 20%</td>
<td>
• Use protamine for partial neutralization (~60%)
<table>
<tr><td>Second dose of protamine (if aPTT remains prolonged 2-4 hrs after first dose)</td></tr>
<tr><td>• May consider 0.5 mg protamine (per 100 units dalteparin or per 1 mg enoxaparin)</td></tr>
</table>
• Degree of reversal can be assessed with Anti-Xa activity (order: “Anti Xa, LMWH”)
<table>
<tr><th colspan="2"></th><th>Dose of protamine</th></tr>
<tr><td rowspan="3">Time since last dose of LMWH</td><td>< 8 hrs</td><td>• 1mg protamine per 100 units of dalteparin
• 1mg protamine per 1mg of enoxaparin
• or 50mg fixed dose</td></tr>
<tr><td>8-12 hrs</td><td>• 0.5mg protamine per 100 units of dalteparin
• 0.5mg protamine per 1mg of enoxaparin
• or 25mg fixed dose</td></tr>
<tr><td>> 12 hrs</td><td>• Not likely to be useful unless CrCl < 30mL/min
• Or 25mg fixed dose</td></tr>
</table>
</td>
</tr>
<tr>
<td>UFH</td>
<td>Heparin</td>
<td>30-90 min (dose dependent)</td>
<td>Partial</td>
<td>• Turn off infusion
• Protamine 50 mg IV</td>
</tr>
<tr>
<td>Vitamin K Antagonist</td>
<td>Warfarin (Coumadin®)</td>
<td colspan="3">General Vitamin K Information:
• Intravenous Vitamin K works faster than oral vitamin K, but is associated with anaphylactic reaction in 3/10,000 patients.
• Subcutaneous injection of vitamin K is not recommended; effect is delayed and unpredictable.
• Use of high doses of vitamin K (e.g., 10 to 15mg) may cause warfarin resistance for ≥1 week.</td>
</tr>
</table>

Serious or life-threatening bleeds (any INR)

- Hold warfarin
- Give vitamin K 10mg IV infusion (over 30 minutes), may repeat in 12 hrs if necessary
- 4-factor PCC (Kcentra™) is preferred over FFP for life-threatening bleeds (see table)
- Give FFP/Plasma if 4-factor PCC unavailable

INR	4-factor PCC Dose
2-4	25 units/kg (max 2500 units)
4-6	35 units/kg (max 3500 units)
> 6	50 units/kg (max 5000 units)

Non-life-threatening bleeds

INR	Clinical Situation	Management
< 4.5	No bleeding	• Hold warfarin
	Rapid reversal required	• Hold warfarin; consider vitamin K 2.5mg oral
4.5 – 10	No bleeding	• Hold warfarin
	Rapid reversal required	• Hold warfarin; consider vitamin K 2.5mg oral or 1mg IV infusion
> 10	No bleeding	• Hold warfarin; consider vitamin K 2.5mg oral or 1-2mg IV infusion
	Rapid reversal required	• Hold warfarin; consider vitamin K 2.5mg oral or 1-2mg IV infusion

Pricing (2019)	4-factor PCC (Kcentra®) for 70 kg pt (50 units/kg; $1.48/unit)	Andexanet alfa (Andexxa®)	Idarucizumab (Praxbind®)
Novation (inpatient)	$5,110	For all 3 accounts: Low dose: $27,500/dose High dose: $49,500/dose	$1,846/dose (2 vials)
340B (outpatient)	$5,180		$1,342/dose (2 vials)
WAC (mixed use)	$5,180		$3,691/dose (2 vials)

G1: Kcentra® Prior Authorization Form

Health Services

4-Factor Prothrombin Complex Concentrate (Kcentra®) Prior Authorization Form

Instructions

1. Please complete all sections of the form. Incomplete forms will be returned to the prescriber.
2. Submit form along with the prescription order to the facility pharmacy. This form is not a substitute for a prescription order. Any form submitted without an order will be considered incomplete and not reviewed.
3. Inpatient use CMO or designee approval is not needed for cases where the criteria are met. If all criteria below are not met, form will be forwarded by the facility pharmacy to DHS Pharmacy Affairs for review. The CMO or designee will provide final decision in these cases.

Notes

1. This prior authorization form must be submitted with **ALL** written inpatient orders.
2. Please complete ALL areas below, as incomplete prior authorization requests **MAY AFFECT THE OUTCOME** of this request.
3. Prothrombin Complex Concentrate is not intended for reversal of the direct thrombin inhibitors.

STEP 1: EXCLUSION CRITERIA *(If any of the following criteria apply, the patient does NOT qualify for 4-Factor Prothrombin Complex Concentrate use (Kcentra®). Check box in step 1 to acknowledge.*

Known anaphylactic or severe systemic reactions to Kcentra® or any components in Kcentra® including heparin, factors II, VII, IX, X, proteins C and S, antithrombin III and human albumin	For the reversal of dabigatran; use of idarucizumab (Praxbind®) may be indicated
Patients with known heparin-induced thrombocytopenia (HIT)	Patients with disseminated intravascular coagulation (DIC)

☐ Patient has none of the exclusion criteria listed above

STEP 2: APPROVAL CRITERIA *(Check ALL criteria that apply; ALL lines must be checked for approval. None of the exclusion criteria above apply.)*
Note: Any incomplete information MAY AFFECT THE OUTCOME of this request.

☐ Patient is currently on warfarin therapy OR factor Xa inhibitors therapy (i.e., rivaroxaban, apixaban, or edoxaban; note that for patients on rivaroxaban or apixaban, use of andexanet (Andexxa®) may be indicated instead of Kcentra®)

☐ Patient requires urgent reversal of VKA anticoagulation OR factor Xa inhibitors and:
- has acute active, life-threatening bleeding (e.g. intracranial hemorrhage) OR
- requires emergency surgical intervention (and supratherapeutic INR in warfarin patients)

☐ Kcentra® will be given in combination with supportive care (i.e. for warfarin associated bleed use IV vitamin K; for factor Xa associated bleed use tranexamic acid or aminocaproic acid; oral activated charcoal an option if last factor Xa inhibitor dose within 2 hours of ingestion)

☐ Only a single dose of Kcentra® will be used

OR

☐ For use in excessive bleeding post cardiopulmonary bypass which is uncontrolled by conventional measures AND

☐ Patient has received at minimum 2 units of fresh frozen plasma and 1 unit of platelets AND

☐ Attending is a cardiac surgeon, or a cardiac anesthesiologist AND

☐ Only a single dose of Kcentra® will be used

STEP 3: DOSAGE *(Check the appropriate dosage)*

Dosing for Patients on Warfarin Therapy	Dosing for Patients on Factor Xa inhibitors (i.e., rivaroxaban, apixaban, edoxaban) *limited data for optimal dose in this setting	Dosing for Excessive Bleeding in Cardiopulmonary Bypass *limited data for optimal dose in this setting
☐ 25 units/kg (2500 units max; recommended in INR 2 to less than 4) ☐ 35 units/kg (3500 units max; recommended in INR 4 to 6) ☐ 50 units/kg (5000 units max; recommended in INR greater than 6)	☐ 25 units/kg (2500 units max) ☐ 50 units/kg (5000 units max)	☐ 25 units/kg (2500 units max)

STEP 4: ADDITIONAL EXPLANATION *(For additional comments, please attach to form)*

STEP 5: PRESCRIBER INFORMATION

Prescriber Name (Printed):		Prescriber Signature: Date: _____ *I declare that the information on this form, to my best knowledge and belief, is true, correct, and complete.*
Prescriber NPI #:	Clinic/Ward:	
Direct Telephone/Pager #:	Email:	

STEP 6: ATTACH TO PRESCRIPTION ORDER

Pharmacy Review: Approval criteria met? ☐ YES ☐ NO See instructions at top of form for next step following review.		
Date Received:	Date of Decision:	
Pharmacist Reviewer:		
Medical Review: ☐ Approved ☐ Denied		
Date Received:	Date of Decision:	
CMO or Designee:		

G2: Andexanet alfa Prior Authorization Form

Coagulation Factor Xa (recombinant), inactivated-zhzo (Andexxa®) Prior Authorization Form

Instructions
1. Please complete all sections of the form. Incomplete forms will be returned to the prescriber
2. Submit form along with the order to the facility pharmacy. This form is not a substitute for an order. Any form submitted without an order will be considered incomplete and not reviewed
3. Inpatient/Clinic/Emergency Department/Operating Room use. CMO or designee approval is not needed for cases where the criteria are met. If all criteria below are not met, form will be forwarded by the facility pharmacy to DHS Pharmacy Affairs for review. The CMO or designee will provide final decision in these cases

Notes
1. This prior authorization form must be submitted with ALL written orders
2. Please complete ALL areas below, as incomplete prior authorization requests MAY AFFECT THE OUTCOME of this request

STEP 1: EXCLUSION CRITERIA *(If any of the following criteria apply, the patient does NOT qualify for Coagulation Factor Xa (recombinant), inactivated-zhzo (Andexxa®))*

Reversal of anticoagulants that are not factor Xa inhibitors	Non-bleeding patient with elevated coagulation tests
Known hypersensitivity reactions to Andexxa® or any components in Andexxa®	Bleeding that can be managed with routine supportive measures only
Last known dose of rivaroxaban or apixaban more than 18 hours ago	Has already received treatment with Andexxa® for this current bleed event

☐ Patient has none of the following exclusion criteria listed above

***Warnings and Precautions** (see Andexxa® package insert for full prescribing information including more detailed warnings, precautions, adverse reactions, and monitoring parameters)*:
1. Black box warning for serious and life-threatening adverse events including arterial and venous thromboembolic events, ischemic events including myocardial infarction and ischemic stroke, cardiac arrest, sudden deaths
2. An improvement in hemostasis has not yet been established
3. Andexxa® has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any factor Xa inhibitors other than apixaban or rivaroxaban.
4. Patients treated with factor Xa inhibitor therapy have underlying disease states that predispose them to thromboembolic events. Reversing factor Xa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. To reduce the risk of thrombosis, resume anticoagulant therapy as soon as medically appropriate following treatment with Andexxa®
5. There are no adequate and well controlled studies in pregnant women; safety and effectiveness has not been evaluated in labor and delivery or pediatric use; and no information regarding presence in human milk, effects on breastfed child, effects on milk production are currently available

***Most common adverse reactions reported include**, urinary tract infections, pneumonia, and infusion related reactions*

STEP 2: APPROVAL CRITERIA *(Check ALL criteria that apply. ALL lines must be checked for approval. None of the exclusion criteria above apply.)*
Note: Any incomplete information **MAY AFFECT THE OUTCOME** of this request.

☐ Last known dose of rivaroxaban or apixaban is within the past 18 hours or unknown **AND**

☐ Only one bolus and one infusion (i.e. no re-dosing and no extension of infusions) **AND**

☐ Attending physician approval (e.g. Hematology, Cardiology, Neurology, Emergency Department, Trauma, Critical Care, Anesthesiology, Neurosurgery) Attending(s): **AND**

☐ Acute overt major bleeding episode requiring urgent reversal of anticoagulation defined as at least one of the following:
1. Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained
2. Acute symptomatic bleeding in a critical area or organ, such as: retroperitoneal, intra-articular or pericardial, intracranial or intramuscular with compartment syndrome
3. Acute overt bleeding associated with a fall in hemoglobin level by 2 g/dL or more, OR a hemoglobin less than or equal to 8 g/dL (if no baseline hemoglobin is available), OR it is the opinion of the attending that the patient's hemoglobin will fall to less than or equal to 8 g/dL with resuscitation

Step 3: Dosing Instructions

Andexxa® Dose Based on Rivaroxaban or Apixaban Dose (Timing of Last Dose of Factor Xa Inhibitor Before Andexxa® Initiation)

Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	Less than 8 Hours or Unknown	8 Hours or more
Rivaroxaban	Less than or equal to 10 mg	Low Dose	Low Dose
	Greater than 10 mg or Unknown	High Dose	
Apixaban	Less than or equal to 5 mg	Low Dose	
	Greater than 5 mg or Unknown	High Dose	

Steph 4: Dosing Regimens *(Please see package insert for infusion instructions and target infusion rates)*

Low Dose	High Dose
☐ 400 mg initial IV bolus followed by an IV infusion of up 480 mg	☐ 800 mg initial IV bolus followed by an IV infusion of up to 960 mg

STEP 5: ADDITIONAL EXPLANATION *(For additional comments, please attach to form)*

STEP 6: PRESCRIBER INFORMATION

Prescriber Name (Printed):		Prescriber Signature Date _____
Prescriber NPI #:	Clinic/Ward ☐ Attending _____ From _____	
Telephone/Pager #	Date:	*I declare that the information on this form, to my best knowledge and belief, is true, correct, and complete*

STEP 7: ATTACH TO ORIGINAL PRESCRIPTION

Pharmacy Review: Approval criteria met? ☐ YES ☐ NO See instructions at top of form for next step following review		
Date Received	Date of Decision	
Pharmacist Reviewer:		
Medical Review:	☐ Approved ☐ Denied	
Date Received	Date of Decision	
CMO or Designee:		