Cardiovascular Drugs and Therapies

ANTICOAGULANTS (Oral)

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1. **Purpose of the Pharmacotherapy Handbook**

   Notice to Healthcare Providers:
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ANTICOAGULANTS (Oral)

Generic Name	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dabigatran**
Trade Name	COUMADIN	ELIQUIS	XARELTO	PRADAXA
Dosing ***UHN Approved Indication***	**Target INR**	**Dose**	**Dose**	**Dose**
Stroke/Systemic embolism Prophylaxis in Atrial Fibrillation	2.5 (2.0-3.0)	5 mg twice daily 2.5 mg twice daily	20 mg once daily with food 15 mg once daily with food	150 mg twice daily 110 mg twice daily
Stroke/Systemic embolism Prophylaxis with Mechanical valves	2.5 (2.0-3.0) *Bioprosthetic aortic/ mitral valve, Mechanical aortic valve (UHN: 2.5-3.0)* 3.0 (2.5-3.5) *Mechanical mitral valve, Mechanical aortic valve with AF, Caged-ball or caged-disk valve, Both aortic and mitral valves (UHN: 3.0-3.5)*	No approved indication	No approved indication	No approved indication
Treatment of DVT, without pulmonary embolism	2.5 (2.0-3.0)* ****Warfarin is approved for both DVT and PE treatment.***	10 mg twice daily for 7 days, followed by 5 mg twice daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily with food	No approved indication

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Dosing Additional Indications	**Target INR**	**Dose**	**Dose**	**Dose**
*Treatment of DVT **AND** pulmonary embolism*	2.5 (2.0-3.0)	10 mg twice daily for 7 days, followed by 5 mg twice daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily with food	**150 mg capsule twice daily following treatment with a parenteral anticoagulant for 5-10 days**
Prevention of VTE in hip (THR) or knee (TKR) replacement surgery	2.5 (2.0-3.0)	2.5 mg twice daily, start 12-24 hours post-op and achieving of hemostasis	10 mg once daily with food, start 24 hours post-op if hemostasis achieved	110 mg, start 1-4 hours post-op and achieving of hemostasis ***or*** 220 mg as single dose when not started day of surgery, regardless of reason Maintenance: 220 mg once daily

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Contraindications and Precautions	Clinically significant active bleeding or risk (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, impairment of hemostasis)	Clinically significant active bleeding or risk (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, impairment of hemostasis)	Clinically significant active bleeding or risk (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, impairment of hemostasis)	Clinically significant active bleeding or risk (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, impairment of hemostasis)
	Pregnant women	Pregnant and nursing women	Pregnant and nursing women	Pregnant and nursing women
	Major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces	Major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces	Major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces	Major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces
	Recent/potential surgery of the eye or CNS	Recent/potential surgery of the eye or CNS	Recent/potential surgery of the eye or CNS	Recent/potential surgery of the eye or CNS
	Severe uncontrolled/ malignant hypertension	Severe uncontrolled/ malignant hypertension	Severe uncontrolled/ malignant hypertension	Severe uncontrolled/ malignant hypertension
	Pericarditis/pericardial effusion	Pericarditis/pericardial effusion	Pericarditis/pericardial effusion	Pericarditis/pericardial effusion
	Bacterial endocarditis	Bacterial endocarditis	Bacterial endocarditis	Bacterial endocarditis

ANTICOAGULANTS (Oral)

Generic Name	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dabigatran**
Contraindications and Precautions, *cont'd*	Advanced age History of falls Genomic variants of CYP2C9 and/or VKORC1: CYP2C9*2 or *3 allele or VKORC1 polymorphism may increase risk of bleeding Purple toe syndrome Necrosis, caution in heparin-induced thrombocytopenia with DVT due to limb ischemia	Advanced age History of falls	Advanced age History of falls	Advanced age History of falls Dyspepsia
Mechanism of Action	Vitamin K antagonist	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Onset	24-72 hours Peak effect: 5-7 days	Peak effect: 3-4 hours	Peak effect: 2-4 hours	Peak effect: 0.5-2 hours
Bioavailability	100%	50%	100% with food 66% in fasting conditions	3-7% in capsule 75% if capsule breached (Do not crush, chew or open capsule)
Half-life	20-60 hours (highly variable)	12 hours	7-11 hours	13 hours

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Metabolism	Hepatic	Hepatic	Hepatic	Hepatic: Cleavage of dabigatran etexilate by esterase-catalyzed hydrolysis to the active drug; undergoes conjugation forming pharmacologically active acylglucuronides
Elimination	Renal (92% as inactive metabolites) Biliary	Renal (25% unchanged) Hepato-biliary/fecal	Renal (50% unchanged) Fecal	Renal (80% unchanged) Biliary
CYP Interaction	Yes (CYP 2C9 substrate)	Yes (CYP 3A4/5 substrate)	Yes (CYP 3A4/5 substrate)	No
PGP Interaction	No	Yes	Yes	Yes

ANTICOAGULANTS (Oral)

Generic Name	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dabigatran**
Clearance Considerations	**Renal** No dose adjustment necessary Chronic kidney disease may increase risk of bleeding complications.	**Renal** SCr ≥133 mmol/L ***AND*** age ≥80 years ***or*** body weight ≤60 kg: Product monograph recommends dose adjustment to 2.5 mg twice daily* CrCl 25-30 mL/min: Generally no dose adjustment necessary, unless patient meets above criteria* CrCl 15-24 mL/min: Limited data available. No dosing recommendation* ** For the treatment of Atrial Fibrillation.* CrCl 15-29 mL/min: Use with caution for the treatment of **DVT without PE** CrCl <15 mL/min or receiving dialysis: Use not recommended, no data available	**Renal** CrCl 30-49 mL/min: 15 mg once daily with food* **For the treatment of Atrial Fibrillation. Treatment of DVT does not require the same dosage adjustment* CrCl <30 mL/min or receiving dialysis: Use not recommended, insufficient safety data available **Hepatic** Contraindicated in Child-Pugh Class B and C	**Renal** CrCl 30-50 mL/min: 110 mg orally twice daily* **For patients aged ≥75 years, and/or other risk factors for bleeding (e.g., moderate renal impairment (CrCl = 30-50 mL/min), concomitant strong P-gp inhibitors, or previous GI bleed*
Clearance Considerations cont				Half-life increases to 27 hours with CrCl 30 mL/min CrCl <30 mL/min or receiving dialysis: Use not recommended, no data available

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Generic Name	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dabigatran**
Monitoring	Frequency of maintenance INR as per INR stability (minimum once every 4 weeks if stable/low-risk bleeding) For patients with consistently stable INRs, an INR testing frequency of up to every 12 weeks rather than every 4 weeks may be considered[13]	Anti-Xa assay: •Sensitive test for detection of anticoagulant effect (linear relation with plasma concentration) •Commercial tests not yet available Serum creatinine, CrCl baseline and every 6-12 months Prothrombin time (PT), international normalized ratio (INR), and the activated partial thromboplastin time (aPTT) are affected in a variable and non-linear manner. Elevations indicate some anticoagulant effect, but do not correlate to degree of anticoagulation.	Anti-Xa assay: •Sensitive test for detection of anticoagulant effect (linear relation with plasma concentration) •Commercial tests not yet available Serum creatinine, CrCl baseline and every 6-12 months Prothrombin time (PT), international normalized ratio (INR), and the activated partial thromboplastin time (aPTT) are affected in a variable and non-linear manner. Elevations indicate some anticoagulant effect, but do not correlate to degree of anticoagulation.	Partial thromboplastin time (aPTT): •>2.5 x control may indicate over-anticoagulation; elevated aPTT indicates some anticoagulant effect, but does not correlate to degree of anticoagulation Serum creatinine, CrCl baseline and every 6-12 months Thrombin time (TT): •Most sensitive test; indicates presence of anticoagulant activity, but does not correlate to degree of anticoagulation •Normal TT (<30 sec) likely indicates no detectable anticoagulant effect Hemoclot test: •Demonstrates direct linear relationship between clotting time & dabigatran concentration •Precise commercial test, not readily available

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Management of Bleeding	IV vitamin K_1 (5-10 mg slow)	No pharmacologic antidote currently available	No pharmacologic antidote currently available	Idarucizumab (Dabigabind) pending FDA approval
		Hemodialysis not useful	Hemodialysis not useful	Hemodialysis may be useful (60% removed over 2-3 hours), data limited
		Activated charcoal can be given within 2-6 hrs of ingestion	Activated charcoal can be given within 1-2 hrs of ingestion	Activated charcoal can be given within 2 hours of ingestion
	4-factor PCCs (i.e., Octaplex®, Cofact®, or rFVIIa [rarely]): options for major bleeding at any INR elevation	PCCs, aPCCs and rFVIIa may be options – limited data available on clinical impact	PCCs, aPCCs and rVIIa may be options– limited data available[7]	PCC (Cofact®) is ineffective
			Four-factor PCC (Cofact®) has been shown to reverse the anticoagulant effect of rivaroxaban	aPCCs, rVIIa or concentrates of FII, IX or X may be options
	FFP or packed RBC			FFP, packed RBC or surgical intervention may be considered for severe hemorrhage
Dosage Forms	Many tablet strengths available	2.5 mg tablet 5 mg tablet	10 mg tablet 15 mg tablet 20 mg tablet	75 mg capsule 110 mg capsule 150 mg capsule
Unit Cost*	$0.08/ 1mg $0.07/ 5 mg $0.12/ 10 mg	$1.60/ 2.5 mg $1.60/ 5 mg	$2.84/ 10 mg $2.84/ 15 mg $2.84/ 20 mg	$1.60/ 110 mg $1.60/ 150 mg
30-Day # Patient Cost	$2.60 (1 mg daily) $2.30 (5 mg daily) $3.90 (10 mg daily)	$104 (2.5, 5 mg bid)	$92 (10, 15, 20 mg daily)	$104 (110, 150 mg bid)

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Generic Name	Warfarin	Apixaban	Rivaroxaban	Dabigatran
ODB[a]	Yes	Yes (Limited Use) **LU = 433 Apixaban 2.5 mg (VTE prevention TKR**) For the prevention of venous thromboembolic events in patients who have undergone elective total knee replacement (TKR) surgery. Note: Limited to 14 days of reimbursement in TKR. Limited to 1 claim in a 120 day period. LU Authorization Period: 1 year. **LU = 434 Apixaban 2.5 mg (VTE prevention in hip replacement**) For the prevention of venous thromboembolic events in patients who have undergone elective total hip replacement (THR). Note: Limited to 35 days of reimbursement in THR. Limited to1 claim in a 120 day period. LU Authorization Period: 1 year. **LU 448 – Apixaban 2.5 mg or 5 mg (AFIB)** INCLUSION CRITERIA: At risk patients with non-valvular atrial fibrillation, for the prevention of stroke and systemic embolism AND in whom: 1. Anticoagulation is inadequate following at least a 2-month trial on warfarin; OR 2. Anticoagulation using	Yes (Limited Use) **LU = 433 (VTE prevention TKR)** For the prevention of venous thromboembolic events in patients who have undergone elective total knee replacement (TKR) surgery. Note: Limited to 14 days of reimbursement in TKR. Limited to 1 claim in a 120 day period. **LU = 434 (VTE prevention in THR)** For the prevention of venous thromboembolic events in patients who have undergone elective total hip replacement (THR). Note: Limited to 35 days of reimbursement in THR. Limited to1 claim in a 120 day period. LU Authorization Period: 1 year. **LU 435 (AFIB)** For the prevention of stroke and systemic embolism in at-risk patients who have non-valvular atrial fibrillation (AF) AND in whom: 1) Anticoagulation is inadequate following a reasonable trial on warfarin; OR 2) Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via International Normalized Ratio (INR) testing (i.e., no access to INR testing service at a laboratory,	Yes (Limited Use) **LU = 431** For the prevention of stroke and systemic embolism in at risk patients with non-valvular atrial fibrillation (AF), AND in whom: 1) Anticoagulation is inadequate following a reasonable trial on warfarin; OR 2) Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via International Normalized Ratio (INR) testing (i.e., no access to INR testing services at a laboratory, clinic, pharmacy, and at home).

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UHN[b] Specific Criteria for Use	Yes	Yes Prevention of stroke and systemic embolism in patients with non-valvular AF with $CHADS_2$ ≥1 and CrCl ≥15 mL/min 2) Treatment of deep vein thrombosis without pulmonary embolism	Yes 1) Prevention of stroke and systemic embolism in patients with non-valvular AF with $CHADS_2$ ≥2 and CrCl ≥30 mL/min 2) Treatment of deep vein thrombosis without pulmonary embolism	Yes Prevention of stroke and systemic embolism in patients with non-valvular AF with $CHADS_2$ ≥1 and CrCl ≥30 mL/min

* List prices from the Ontario Drug Benefit (ODB) Formulary, Ontario Ministry of Health. Last Updated: 01/04/2011 Version 2.2. All prices represent the generic medication option, where it exists.
# 30-day patient costs represented by ODB generic price + 8% markup. These prices do not include a dispensing fee, which can range from $4.99 to $11.99. Pricing is based on a typical dosing regimen.
a - ODB – indicates an item on the Ontario Drug Benefit (ODB) Formulary
b - UHN - indicates an item on the University Health Network Formulary

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