APIXABAN CLINICIAN SUMMARY

Mechanism of Action: Direct Factor Xa Inhibitor

BACKGROUND

Apixaban is a direct Factor Xa inhibitor that is administered orally. It inhibits both free Factor Xa and Factor Xa bound to prothrombinase.

Apixaban is indicated in Canada for:

- prevention of stroke and systemic embolism in patients with atrial fibrillation
- prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery
- treatment of venous thromboembolism (deep venous thrombosis (DVT), pulmonary embolism (PE)) and prevention of recurrent DVT and PE

Place in Therapy at UHN

Apixaban is approved at UHN for:

- prevention of stroke and systemic embolism in patients with atrial fibrillation and a $CHADS_2$ score greater or equal to 1
- treatment of DVT without symptomatic PE

Dose for ATRIAL FIBRILLATION

- **Usual dose:** 5 mg twice daily
- **Low dose:** 2.5 mg twice daily (recommended for patients that have any 2 of the following: serum creatinine $\geq$133 micromol/L, age ≥80 years old, body weight ≤60 kg)

Dose for TREATMENT of DVT without symptomatic PE

- Treatment: 10 mg twice daily for 7 days followed by 5 mg twice daily

Administration

Can be administered with or without food.

Pharmacologic Profile

Onset	Immediate (3-4 hours)
Peak effect	3-4 hours
Bioavailability	Approximately 50% Not affected by food (C_{max} or AUC)
Half-life	8 hours (2.5 mg repeated oral dose) 15 hours (5 mg single dose)
Distribution	Highly protein bound (approximately 87-93%)
Metabolism	Predominantly hepatic through CYP3A4/5, with minor contributions through CYP1A2, 2C8, 2C9, 2C19, 2J2 P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) substrate
Elimination	75% via the hepatobiliary system (with 25% recovered as metabolites) 25% via renal excretion

Laboratory Monitoring

- Routine laboratory monitoring of apixaban to assess efficacy is not indicated.

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- Apixaban will prolong common coagulation screening tests, such as the prothrombin time (PT), international normalized ratio (INR), and the activated partial thromboplastin time (aPTT) in a variable and non-linear manner.
- There is a direct linear relationship between anti-Factor Xa activity and apixaban concentration, therefore, the anti-Factor Xa assay may be useful in the assessment of apixaban concentration in the future.
- Serum creatinine, creatinine clearance (CrCl) at baseline and every 6-12 months

Contraindications

- Clinically significant active bleeding (including gastrointestinal bleeding)
- Lesions or conditions at risk of clinically significant bleeding (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Concomitant systemic treatment with strong inhibitors of CYP3A4 and P-gp (e.g., azole antimycotics, HIV protease inhibitors)
- Concomitant treatment with any other anticoagulation including unfractionated heparin (except at doses used to maintain patency of central venous or arterial catheter), low molecular weight heparins, heparin derivatives (i.e., fondaparinux), and oral anticoagulants including warfarin, dabigatran andrivaroxaban except when transitioning to or from apixaban therapy
- Hypersensitivity to apixaban or any component of the formulation

PRECAUTIONS

Drug interactions

- Strong dual inducers of both CYP3A4 and P-gp, such as rifampin, phenytoin, carbamazepine, phenobarbital, or St. John's Wort, may lead to a ~50% reduction in apixaban exposure. Co-administration is cautioned.
- Concomitant use of agents that increase bleeding risk should be avoided or used with caution (i.e., platelet aggregation inhibitors, antithrombotics, NSAIDs [e.g., ASA, ibuprofen, naproxen])

Renal Impairment

Creatinine Clearance (mL/min)	Dose Recommendations
CrCl <30 mL/min	**For Atrial Fibrillation** Dose adjustment to low dose regimen recommended for patients that have any 2 of the following: serum creatinine ≥133 micromol/L, age ≥80 years old, body weight ≤60 kg • CrCl 15-24 mL/min, limited data available. Bleeding risk may be higher in patients with severe renal impairmentas apixaban plasma concentration increases **For treatment of deep vein thrombosis and/or pulmonary embolism**

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	• CrCl 15-29 mL/mon, use with caution. Bleeding risk may be higher in patients with severe renal impairment
CrCl <15 mL/min or receiving dialysis	• Use not recommended, no data available

Hepatic impairment
- Avoid use in severe hepatic impairment (Child-Pugh class C)
- Caution use in mild/moderate impairment (Child-Pugh class A or B) due to limited data in clinical trials

Acute coronary syndrome
- In high-risk post-acute coronary syndrome patients,[7] apixaban 5 mg twice daily as an adjunct to standard antiplatelet treatment significantly increased bleeding without a reduction in ischemic events
- There is no specific indication for apixaban in patients with recent ACS

Valvular Disease
- Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves or hemodynamically significant rheumatic heart disease. The use of apixaban is not recommended in this setting

Pregnancy/Lactation/Pediatrics
- Due to lack of human safety and efficacy data, apixaban is not recommended during pregnancy/lactation nor in the pediatric population

Adverse Effects
- Bleeding
- Significant safety endpoints from the ARISTOTLE trial:[2]
  Compared to warfarin, apixaban demonstrated:
  - Significantly **lower** rates of major and clinically relevant non-major bleeding
  - Significantly **lower** rates of intracranial bleeding and other location bleeding
  - Significantly **lower** rates of all-cause mortality
  - Similar rates of gastrointestinal bleeding
  - Lower discontinuation rates
- Significant safety endpoints from the AVERROES trial:[3]
  Compared to aspirin, apixaban demonstrated:
  - Similar rates of major bleeding
  - Lower discontinuation rates

Switching from Other Agents *to* Apixaban

Agent	Recommendation
Intermittent parenteral anticoagulants *(e.g., low molecular weight heparin, fondaparinux)*	Start apixaban at the next scheduled dose of the parenteral anticoagulant

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Continuous parenteral anticoagulants *(e.g., heparin)*	Start apixaban at the time of heparin discontinuation
Warfarin	Discontinue warfarin and start apixaban when INR <2.0
Dabigatran	Start apixaban *12 hours* after the last dose of dabigatran
Rivaroxaban	Start apixaban *24 hours* after the last dose of rivaroxaban *Consider starting apixaban as early as 12 hours after the last dose of rivaroxaban for patients with normal renal function (CrCl >50 mL/min) who are at greater risk of stroke (e.g., high $CHADS_2$ score, recent cardioversion, etc.)*

Switching *from* Apixaban to Other Agents

Agent	Recommendation
Intermittent or continuous parenteral anticoagulants *(e.g., low molecular weight heparin, fondaparinux, heparin)*	Start parenteral anticoagulant at the next scheduled dose of apixaban
Warfarin	Apixaban affects the INR. Measurement of INR when apixaban and warfarin are used concomitantly may not be useful for determining an appropriate dose of warfarin Two strategies: • Discontinue apixaban and start parenteral anticoagulants (as bridging therapy for warfarin) and warfarin at the time of the next apixaban dose. Discontinue the parenteral anticoagulant when the INR is therapeutic ***or*** • Initiate warfarin at usual starting doses and continue apixaban until INR $\geq$2.0, then discontinue apixaban. During concomitant therapy, the manufacturer recommends initiating INR testing on day 3 and just prior to each dose of apixaban
Dabigatran	Start dabigatran *12 hours* after the last dose of apixaban
Rivaroxaban	Start rivaroxaban *12 hours* after the last *morning* dose of apixaban (approved FDA labeling recommends administration of rivaroxaban with the evening meal in the absence of data indicating otherwise)

Neuraxial Anesthesia and Apixaban

There is limited experience with the use of Factor Xa inhibitors with neuraxial anesthesia. When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics are at risk for developing epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis. Traumatic or repeated epidural or spinal puncture also increases the risk of these events.

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- As with other Factor Xa inhibitors, we recommend discontinuation of apixaban 5 days prior to neuraxial intervention. The first dose of apixaban may be administered not earlier than 6 hours following spinal anesthesia, lumbar plexus block, or epidural catheter removal.
- Apixaban should not be administered to patients with an indwelling epidural catheter; in the event an epidural catheter is *in situ*, it should be withdrawn **no earlier than 24 hours** after the last administered dose of apixaban.
- Patients who have undergone epidural puncture and who are receiving apixaban should be monitored frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of legs, bowel or bladder dysfunction).

Periprocedural/Perioperative Management
Consider both the risk of bleeding in the patient and the surgical bleeding risk.

Please refer to the UHN Periprocedural Hemostasis Policy & Procedures:
http://documents.uhn.ca/sites/uhn/Policies/Clinical/Blood_Transfusion/3.130.009.pdf

Hold apixaban as per patient's creatinine clearance:

Calculated Creatinine Clearance	Last dose pre-procedure	
	Procedures with low risk of bleeding	Procedures with moderate to significant risk of bleeding
Greater or equal to 50 mL/min	24 hours	2 days
Less than 50 mL/min	At least 2 days	At least 4 days

** see list of procedures and bleed risk under UHN Periprocedural Hemostasis Policy*
Note: Basic cardiac catheterizations could be a procedure with low risk of bleeding, but other factors or catheterisation procedures could be high risk procedures, check with the operator or cardiac triage to determine risk of bleeding

When Is Bridging Required?
As per UHN Periprocedural Hemostasis Policies, consult hematology for discussion of bridging anticoagulation in patients with:
- mechanical heart valves
- Atrial fibrillation with prior neurologic event
- Recent (less than 3 months ago) venous thromboembolism
- Intracardiac thrombus
- Antiphospholipid syndrome

When to Resume Apixaban Post-procedure
Time to resume apixaban depends on the postoperative risk of bleeding.

When apixaban has been withdrawn for an invasive procedure, therapy can be restarted 1 day after hemostasis is established post-procedure. (usually 48 hours for a procedure with a low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding).[10]

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For procedures such as major abdominal surgery or urologic surgery with incomplete hemostasis, apixaban should only be resumed when there is no drainage or other evidence of active bleeding.

Acute Management of Acute Coronary Syndromes (ACS)
For patients who arrive in the Emergency Department on apixaban and who need treatment for ACS:

- Treatment should follow usual clinical practice.
- Consideration should be given to temporarily suspend apixaban in the setting of ACS, due to need for invasive procedures, such as PCI or CABG, or if thrombolytic therapies are to be initiated.
- Timing, choice, and dose of parenteral anticoagulation should be balanced against last intake of apixaban and risk of bleeding, noting that apixaban has a short half-life of 8-15 hours in normal renal function. Recent intake (i.e., within 8 hours) may increase the risk of bleeding when initiating parenteral full-dose anticoagulation.

ASPIRIN THERAPY
Always re-assess indication for ASA when starting apixaban. If it was previously prescribed for the sole indication of stroke prevention in atrial fibrillation, ensure ASA is discontinued when apixaban is initiated.

Management of Bleeding Complications or Reversal of Apixaban
- Contact Poison Control Centre for the most up-to-date guidelines
- There is currently no antidote available. Phase III trials underway for antidote: andexanet alfa
- Expert opinion suggests the following:
  - Delaying or withholding further doses. Providing supportive care is sufficient in most cases, given apixaban's short half-life (12 hours)
  - For overdoses, activated charcoal may be considered if given within 2-6 hours of ingestion to prevent further drug absorption
- Supportive measures:
  - Maintain diuresis (with renally cleared drugs)
  - Mechanical compression
  - Surgical intervention
  - Fluid resuscitation
- Hemodialysis is not a useful option, since apixaban is highly protein bound.
- Transfusion of blood products:
  - Hematology Service should be consulted in cases of life-threatening bleeding, to assist in the administration of blood products and reversal agents, such as: Prothrombin complex concentrates (PCCs), activated prothrombin complex concentrates (aPCCs), e.g., FEIBA
  - Recombinant Factor VIIa (rFVIIa), e.g., NovoSeven
- There is currently very limited experience with the use of these products in individuals receiving apixaban. Further studies are required to determine their clinical impact.

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Prepared by: Jessica Koo, BScPhm, ACPR, Pauline Ng, Pharmacy Student – March 2013
Reviewed by: Laura Murphy, PharmD, Rita Selby, MD – April 2013
Approved by: Cardiovascular Subcommittee – April 2013;
Pharmacy & Therapeutics Committee – May 2013
Updated by: Caitlin Meyer, BScPhm, ACPR – January 2015
Updated by: Amanda Chan, BScPhm, ACPR, Jessica Koo, BScPhm, ACPR – November 2015

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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