In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR** to **warfarin** for the reduction in combined stroke and systemic embolism (primary efficacy endpoint)

21% RRR

1.27%/year vs. warfarin 1.60%/year;
HR 0.79, 95% CI: 0.66-0.95, p=0.0114[2*]

For systemic embolism: HR 0.87, 95% CI: 0.44-1.75

In patients with atrial fibrillation, **ELIQUIS** was demonstrated to be **SUPERIOR** to **warfarin** for major bleeding (primary safety endpoint)

31% RRR

2.13%/year vs. warfarin 3.09%/year;
HR 0.69, 95% CI: 0.60-0.80, p<0.0001[2*†]

Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from the ARISTOTLE and AVERROES trials, and thus were not evaluated. These trial results do not apply to these patients, with or without atrial fibrillation.[2]

As with all anticoagulants, ELIQUIS should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with ELIQUIS. The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. An unexplained fall in hemoglobin, hematocrit or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed ELIQUIS. **Should severe bleeding occur, treatment with ELIQUIS must be discontinued and the source of bleeding investigated promptly.** Close clinical surveillance (i.e., looking for signs of bleeding or anemia) is recommended throughout the treatment period. This may include looking for obvious signs of bleeding, e.g., hematomas, epistaxis, or hypotension, testing for occult blood in the stool, checking serum hemoglobin for significant decrease, etc., especially if other factors/conditions that generally increase the risk of hemorrhage are also present.[2]

Bleeding of any type was observed at a rate of 18% per year in AF patients. Common adverse reactions with ELIQUIS were epistaxis (6.2%), contusion (5.0%), hematoma (2.6%), hematuria (3.7%), hemorrhage (including eye [2.3%], gastrointestinal [2.1%], rectal [1.6%] and other [1.7%]) and gingival bleeding (1.2%).[2]

RRR = relative risk reduction, HR = hazard ratio, CI = confidence interval

* Randomized, double-blind, parallel-arm, non-inferiority trial in 18,201 patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation or atrial flutter and ≥1 of the following additional risk factors: prior stroke, transient ischemic attack or systemic embolism, age ≥75 years, arterial hypertension requiring treatment, diabetes mellitus, heart failure (NYHA Class ≥2), decreased left ventricular ejection fraction. Patients received apixaban 5 mg BID (n=9,120, 2.5 mg BID in a subset of patients with ≥2 of the following criteria: ≥80 years, body weight ≤60 kg or a serum creatinine level ≥133 µmol/L) or warfarin (n=9,081) at a target INR range of 2.0-3.0 for a median of 90 weeks for apixaban and 88 weeks for warfarin. The median time in therapeutic range for subjects randomized to warfarin, excluding the first 7 days of the study and excluding warfarin interruptions, was 66%. The primary objective of the study was to determine if apixaban was non-inferior to warfarin for the prevention of total stroke (ischemic, hemorrhagic or unspecified) and systemic embolism. Key study outcomes were assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial. The intention-to-treat (ITT) population was used for efficacy outcome testing, the on-treatment population for safety outcomes.[2]

† Major bleeding was defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of ≥2 g/dL or transfusion of ≥2 units of packed red cells, occurring at a critical site, or resulting in death.[5] Dataset includes events occurring on-treatment plus the following 2 days. Concomitant aspirin use with either ELIQUIS or warfarin increased the risk of major bleeding 1.5 to 2 times when compared with those patients not treated with concomitant aspirin. ELIQUIS, like other anticoagulants, should be used with caution in patients treated concomitantly with antiplatelet agents.[2]

Pr Eliquis® apixaban

In patients with CrCl >25 mL/min, no dosage adjustment necessary unless 2 of the ABC criteria are met[2*]

Clinical use:

Safety and efficacy not established in pediatric patients (<18 years); therefore, Health Canada has not authorized an indication for pediatric use.

Contraindications:

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Concomitant systemic treatment with strong inhibitors of **both** CYP3A4 and P-glycoprotein
- Concomitant treatment with any other anticoagulant including unfractionated heparin, except at doses used to maintain a patent central venous or arterial catheter, low molecular weight heparins, such as enoxaparin and dalteparin, heparin derivatives, such as fondaparinux, and oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, except under circumstances of switching therapy to or from apixaban

Most serious warnings and precautions:

- **Bleeding:** if severe, discontinue
- **Peri-operative spinal/epidural anesthesia, lumbar puncture:** increased risk of hematoma
- **INR monitoring:** not a valid measure to assess anticoagulant activity of ELIQUIS
- **Premature discontinuation:** increases risk of thrombotic events

Other relevant warnings and precautions:

- Caution when used with drugs that affect hemostasis
- Not recommended in patients with prosthetic heart valves or with hemodynamically significant rheumatic heart disease, especially mitral stenosis
- Avoid use with strong inducers of both CYP3A4 and P-gp
- Caution in patients with mild or moderate hepatic impairment (not recommended if severe) or elevated liver enzymes
- Pre-operative/post-operative considerations
- Not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS)
- Renal impairment: not recommended if creatinine clearance <15 mL/min or dialysis; dosing adjustments may be required; renal function should be monitored
- Not recommended in pregnant or nursing women

For more information:

Please consult the Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/ELIQUIS_EN_PM.pdf or https://www.pfizer.ca/pm/en/eliquis.pdf for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-866-463-6267.

* **ABC** criteria: dose reduction to 2.5 mg BID if at least 2 of the following: **a**ge ≥80 years, **b**ody weight ≤60 kg, **c**reatinine level ≥133 µmol/L.

References: 1. IMS Brogan, Compuscript, July 2019. **2.** ELIQUIS Product Monograph. Pfizer Canada ULC and Bristol-Myers Squibb Canada Co. **3.** Lixiana Product Monograph. Servier Canada Inc., July 26, 2017. **4.** Xarelto Product Monograph. Bayer Inc., September 20, 2019. **5.** Granger CB *et al.*; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92. **6.** Pradaxa Product Monograph. Boehringer Ingelheim Canada Ltd., September 16, 2019.

Pfizer Canada ULC, Kirkland, Quebec H9J 2M5
Bristol-Myers Squibb Canada Co., Montreal, Quebec H4S 0A4

Printed on paper derived from 30% post-consumer waste.

MEMBER OF INNOVATIVE MEDICINES CANADA

PAAB

Bristol-Myers Squibb

Pfizer

PP-ELI-CAN-0342-EN
1416675

Pr ELIQUIS® #1 DISPENSED NOAC IN CANADA[1*]

ELIQUIS is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF).

NOAC = non-vitamin K antagonist oral anticoagulant
* Comparative clinical significance unknown.

Pr Eliquis® apixaban

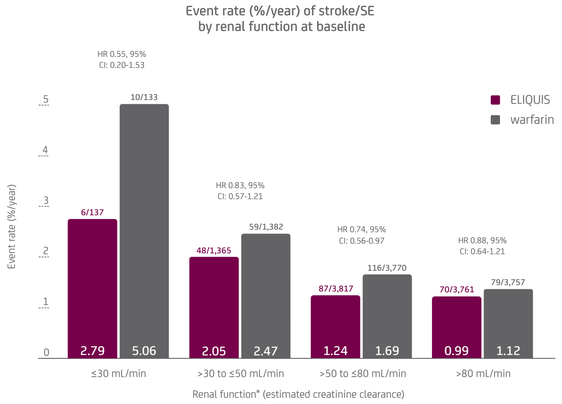
Renal excretion and increase in exposure (AUC) of select Factor Xa inhibitors by level of renal impairment*†

	Renal excretion of unchanged drug	Increase of plasma concentrations (AUC) of select Factor Xa inhibitors by level of renal impairment		
		Mild (CrCl)	Moderate (CrCl)	Severe (CrCl)
Pr ELIQUIS® (apixaban)[2]	**27%**	**16%** (51-80 mL/min)	**29%** (30-50 mL/min)	**44%** (15-29 mL/min)
Pr Lixiana® (edoxaban)[3]	**50%**	**32%** (50-80 mL/min)	**74%** (30-50 mL/min)	**72%** (<30 mL/min)
Pr Xarelto® (rivaroxaban)[4]	**~33%**	**40%** (50-79 mL/min)	**50%** (30-49 mL/min)	**60%** (15-29 mL/min)

AUC = area under the curve; CrCl = creatinine clearance
* Comparative clinical significance unknown.
† Relative to subjects with normal renal function.

Adapted from respective Product Monographs[2-4]

Combined stroke and SE results in AF renal subgroups[2]

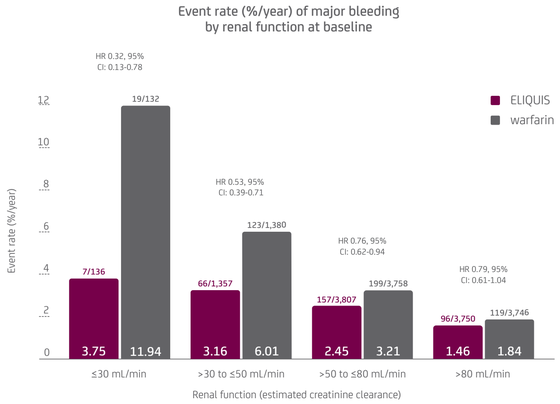


Adapted from Product Monograph[2]

Determine estimated creatinine clearance (eCrCl) in all patients before instituting ELIQUIS. ELIQUIS is not recommended in patients with creatinine clearance <15 mL/min, or in those undergoing dialysis. In AF patients, no dose adjustment is necessary in the elderly (>65 years), in patients with mild or moderate renal impairment, or in those with eCrCL 25-30 mL/min, unless the criteria for dose reduction are met. Patients with ≥2 of the "ABC" criteria should receive 2.5 mg BID (age ≥80 years, body weight ≤60 kg, creatinine level ≥133 µmol/L).[2]

* Patients with eCrCl <25 mL/min at baseline were excluded from the trial.[2]

Major bleeding results (primary safety endpoint) in AF renal subgroups[2]



Adapted from Product Monograph[2]

- Rate of fatal bleeding in patients with eCrCl >50 to ≤80 mL/min: HR 1.70, 95% CI: 0.43-7.94 (0.06%/year for warfarin vs. 0.11%/year for ELIQUIS)[2]

AF dosage and administration for select oral anticoagulants*

	Administration with food	Recommended dose in AF	Creatinine clearance	Dosage adjustments
Pr**ELIQUIS®** (apixaban)[2]	**Can be taken with OR without food**	**5 mg BID**	Mild: >50 to ≤80 mL/min Moderate: >30 to ≤50 mL/min Severe: ≥25 to ≤30 mL/min	5 mg BID Dose adjustment to 2.5 mg BID only if ≥2 of **ABC**† criteria (**a**ge ≥80 years, **b**ody weight ≤60 kg, **c**reatinine level ≥133 µmol/L) are met
			≥15 to ≤24 mL/min	No dosing recommendation can be made as clinical data are very limited
			<15 mL/min or undergoing dialysis	Not recommended
				Not recommended in patients with severe hepatic impairment; contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Pr**Lixiana®** (edoxaban)[3]	**Can be taken with OR without food**	**60 mg QD**	Moderate: 30-50 mL/min Severe: <30 mL/min	30 mg QD Not recommended
				Patients with ≥1 of the following criteria should receive 30 mg QD: moderate renal impairment (CrCl: 30-50 mL/min), low body weight (≤60 kg [132 lbs]), concomitant use of P-gp inhibitors (except amiodarone and verapamil) Not recommended in patients with severe hepatic impairment
Pr**Pradaxa®** (dabigatran)[6]	**Can be taken with OR without food**	**150 mg BID**	Moderate: 30-50 mL/min	No dose adjustment generally needed
				Patients ≥80 years should receive 110 mg BID At higher risk of bleeding, including elderly ≥75 years with ≥1 risk factor for bleeding, 110 mg BID. May also be considered for patients taking concomitant anti-platelet agents or P-gp inhibitors Not recommended in patients with hepatic impairment (hepatic enzymes >ULN); contraindicated in patients with severe renal impairment
Pr**Xarelto®** (rivaroxaban)[4]	**Must be taken with food**	**20 mg QD**	Moderate: 30-49 mL/min Severe: 15 to <30 mL/min	15 mg QD
			<15 mL/min	Not recommended
				Use with caution in patients with moderate hepatic impairment; contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk

eCrCl = estimated creatinine clearance

* Comparative clinical significance unknown.

† These patients have been determined to be at higher risk of bleeding.

Adapted from respective Product Monographs[2,4,6]