Drug Monograph

Drug/Drug Class: **Eliquis™ (apixaban) tablet / factor Xa anticoagulant**

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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 2.5 mg tablet of Eliquis contains 2.5 mg of apixaban and each 5 mg tablet contains 5 mg of apixaban. Bristol-Myers Squibb Company Princeton, New Jersey 08543 USA
Summary of Findings:	Eliquis is a factor Xa inhibitor anticoagulant that has demonstrated efficacy in reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ No PA Required ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

With a diagnosis of nonvalvular atrial fibrillation, anticoagulation therapy is necessary. Development of oral medications that do not require regular laboratory monitoring that are also efficacious is highly beneficial for this patient population.

Dosage Form(s) [1]

Each 2.5 mg tablet of Eliquis contains 2.5 mg of apixaban and each 5 mg tablet of Eliquis contains 5 mg of apixaban.

Manufacturer

Bristol-Myers Squibb Company Princeton, New Jersey 08543 USA

Indication(s) [1]

Eliquis is FDA approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Clinical Efficacy[1-13] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1,2)

Eliquis is an oral, reversible, and selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Eliquis inhibits free and clot-bound factor Xa, and prothrombinase activity. It has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, Eliquis decreases thrombin generation and thrombus development.

PHARMACOKINETICS (1,5)

Eliquis is 87% protein bound with a volume of distribution of 21 L. It is metabolized by the liver, mainly via CPY3A4 and excreted in both urine and feces with a half-life of 12 hours.

EFFICACY (1-13)

SUMMARY

The approval of Eliquis was primarily based upon a multinational, randomized, double-blind clinical trial (ARISTOTLE) involving more than 18,000 patients with nonvalvular AF that compared the effects of Eliquis and warfarin on the risk of stroke and non-CNS systemic embolism. Results from this study showed Eliquis was superior to warfarin in reducing the risk

of stroke and systemic embolism and also showed significantly fewer major bleeds than warfarin. In a second randomized, comparative clinical trial (AVERROES) involving approximately 5600 patients with nonvalvular AF who were not candidates for warfarin therapy, Eliquis was found to be statistically superior to aspirin for preventing the composite outcome of stroke or systemic embolism, and the study was stopped early based upon a prespecified interim analysis. Direct clinical comparisons between Eliquis and dabigatran or rivaroxaban are not available.

STROKE AND SYSTEMIC EMBOLISM PREVENTION - ARISTOTLE TRIAL

STUDY DESIGN	Multinational, randomized, double-blind clinical trial (n=18,201).
INCLUSION CRITERIA	Patients with nonvalvular AF. Patients had to have one or more of the following additional risk factors for stroke: 1) a prior stroke or transient ischemic attack (TIA), 2) a prior systemic embolism, 3) age >= 75 years, 4) arterial hypertension requiring treatment, 5) diabetes mellitus, 6) heart failure that was >= New York Heart Association Class 2, or 7) a left ventricular ejection fraction of <= 40%.
EXCLUSION CRITERIA	Key exclusion criteria were atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation, a stroke within the previous 7 days, a need for aspirin at a dose of > 165 mg/day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine > 2.5 mg/dL (221 mcmol/L) or a calculated creatinine clearance of < 25 mL/min).
TREATMENT REGIMEN	Patients were randomized to Eliquis 5 mg orally twice daily or warfarin, which was targeted to an INR range of 2 to 3, and followed for a median of 89 weeks. Patients with at least 2 of the following characteristics received Eliquis 2.5 mg twice daily: age >= 80 years, body weight <= 60 kg, or serum creatinine >= 1.5 mg/dL. The primary objective was to determine whether Eliquis was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. The superiority of Eliquis to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause. Forty-three percent of patients were vitamin K antagonist (VKA) naive, which was defined as having received <= 30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean CHADS2 score was 2.1. Using a scale of 0 to 6, the CHADS2 estimates the risk of stroke, with higher scores predicting a greater risk. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases included hypertension 88%, diabetes 25%, congestive heart failure (or a left ventricular ejection fraction of <= 40%) 35%, and prior myocardial infarction 14%. The patients treated with warfarin had a mean percentage of time in therapeutic range (INR 2 to 3) of 62%.
RESULTS	Eliquis was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism. The incidence of stroke or systemic embolism

	was 1.27%/year for patients receiving Eliquis compared with 1.6%/year for warfarin (Hazard Ratio (HR), 0.79; 95% CI, 0.66 to 0.95; p=0.01). The superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared with warfarin. Purely ischemic strokes occurred with similar rates for both drugs. Eliquis also showed significantly fewer major bleeds than warfarin. All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus, major bleeding) were demonstrated. Eliquis treatment resulted in a significantly lower rate of all-cause death (p=0.046) than warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.
SAFETY	The most common adverse reactions were related to bleeding. The incidence of major bleeding was 2.13%/year for apixaban compared with 3.09%/year for warfarin (p < 0.0001).

STROKE AND SYSTEMIC EMBOLISM PREVENTION - AVERROES TRIAL

STUDY DESIGN	Multicenter, randomized, double-blind clinical trial (n=5599).
INCLUSION CRITERIA	Patients with nonvalvular AF who were not candidates for warfarin therapy.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to Eliquis 5 mg orally twice daily (or 2.5 mg twice daily in select patients) or aspirin 81 mg to 324 mg once daily. The primary objective was to determine if Eliquis was superior to aspirin for preventing the composite outcome of stroke or systemic embolism.
RESULTS	The AVERROES trial was stopped early on the basis of a prespecified interim analysis that showed a significant reduction in stroke and systemic embolism for Eliquis when compared with aspirin that was associated with a modest increase in major bleeding. The incidence of stroke or systemic embolism was 1.62%/year in patients receiving Eliquis compared with 3.63%/year for aspirin (HR, 0.45; 95% CI, 0.32 to 0.62; p < 0.0001).
SAFETY	The most common adverse reactions were related to bleeding. The incidence of major bleeding was 1.41%/year in the Eliquis group compared with 0.92%/year for aspirin (p=0.07).

Contraindications[1]

- Active pathological bleeding.
- Severe hypersensitivity to Eliquis.

Warnings and Precautions[1]

- Increased risk of stroke with discontinuation is possible in the absence of adequate alternative anticoagulation; if Eliquis must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.
- Serious, potentially fatal bleeding may occur; promptly evaluate signs and symptoms of blood loss.
- Not recommended for patients with prosthetic heart valves.

Adverse Effects[1]

Bleeding events, ARISTOTLE Trial	**Eliquis (n=9088) %/year**	**Warfarin (n=9052) %/year**
▪ Major bleeding	2.13%	3.09%
▪ Gastrointestinal bleeding	0.83%	0.93%
▪ Intracranial bleeding	0.33%	0.82%
▪ Intraocular bleeding	0.21%	0.14%
▪ Fatal bleeding	0.06%	0.24%
▪ Non-major bleeding	2.08%	3.00%
Bleeding events, AVERROES Trial	**Eliquis (n=2798) %/year**	**Aspirin (n=2780) %/year**
▪ Major bleeding	1.41%	0.92%
▪ Fatal bleeding	0.16%	0.16%
▪ Intracranial bleeding	0.34%	0.35%

Drug Interactions[1]

- Anticoagulants
- Antiplatelets
- Strong dual CYP3A4 and P-gp inducers: carbamazepine, phenytoin, rifampin, St. John's wort
- Strong dual CYP3A4 and P-gp inhibitors: clarithromycin, itraconazole, ketoconazole, ritonavir

Dosage and Administration[1]

The recommended dose is 5 mg orally twice daily. A lower dose of 2.5 mg twice daily is recommended for patients with at least 2 of the following characteristics: age >= 80 years, body weight <= 60 kg, or a serum creatinine >= 1.5 mg/dL.

Cost Comparisons (at commonly used dosages)

COST

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Apixaban	Eliquis	Bristol-Myers Squibb	2.5 mg tablets	1 tablet twice	$ 250.20

				daily	
			5 mg tablets	1 tablet twice daily	$ 250.20
Dabigatran	Pradaxa	Boehringer Ingelheim	75 mg capsules	1 capsule twice daily	$ 300.44
			150 mg capsules	1 capsule twice daily	$ 300.44
Rivaroxaban	Xarelto	Janssen	15 mg tablets	1 tablet once daily	$ 300.42
			20 mg tablets	1 tablet once daily	$ 300.42

*Wholesale Acquisition Cost (WAC)

Conclusion

Eliquis is a factor Xa inhibitor anticoagulant that has demonstrated efficacy in reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. It is the third oral anticoagulant to be recently approved in the United States for this indication. Eliquis and the direct thrombin inhibitor, dabigatran, are dosed twice daily, while rivaroxaban, a factor Xa inhibitor, is given once daily. All 3 of these agents do not require regular laboratory monitoring of coagulation, and they have a lower propensity for drug interactions when compared with warfarin. However, there are no agents available that can reverse the anticoagulant effects. Furthermore, direct clinical comparisons between these agents are not available and would be helpful in differentiating the products. The US Food and Drug Administration has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of Eliquis outweigh the potential risks.

Recommendation

The Division recommends this product be considered for inclusion in the state specific Preferred Drug List and is currently under solicitation.

References

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