Drug Monograph

Drug/Drug Class:	**Savaysa™ (edoxaban tosylate) tablets/ Anticoagulants**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **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:	Savaysa™ is available in a film coated tablet containing 15 mg, 30 mg, or 60 mg of edoxaban tosylate. Daiichi Sankyo, Inc. Parsippany, NJ 07054
Summary of Findings:	The approval of Savaysa was based upon two multinational, randomized, double-blind clinical trials. In the ENGAGE AF-TIMI 48 trial in 21,105 patients with nonvalvular atrial fibrillation, Savaysa was noninferior to warfarin in reducing the risk of stroke and systemic embolism (yearly event rate, 1.18% vs 1.5%). Savaysa was associated with significantly lower rates of major bleeding (yearly event rate, 2.75% vs 3.43%) compared with warfarin, except for a higher annualized rate of major gastrointestinal bleeding (yearly event rate, 1.51% vs 1.23%). In the Hokusai-VTE trial in 8292 patients with acute symptomatic venous thromboembolism (VTE), Savaysa was noninferior to warfarin for symptomatic recurrent VTE (event rate, 3.2% vs 3.5%) and had a significantly lower rate of clinically relevant non-major bleeding (7.2% vs 8.9%) compared with warfarin.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ 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[4,5]

Nonvalvular atrial fibrillation is a type of irregular heartbeat. People with atrial fibrillation are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. Blood clots called deep vein thrombi (DVT) often develop in the deep leg veins. Pulmonary embolism (PE) occurs when clots break off from vein walls and travel through the heart to the pulmonary arteries. The broader term venous thromboembolism (VTE) refers to DVT, PE, or to a combination of both. VTE poses a public health threat with an estimated incidence in the United States of 250,000 to 2 million cases per year.

Dosage Form(s) [1]

Savaysa™ is available in a film coated tablet containing 15 mg, 30 mg, or 60 mg of edoxaban tosylate.

Manufacturer [1]

Daiichi Sankyo, Inc., Parsippany, NJ 07054

Indication(s) [1]

Savaysa™ is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the treatment of DVT and PE after 5 to 10 days of treatment with a parenteral anticoagulant.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Savaysa™ is a selective inhibitor of factor Xa and does not require antithrombin III for activity. It decreases generation of thrombin and thrombus formation by inhibiting free factor Xa, prothrombinase activity, and thrombin-induced platelet aggregation.

Pharmacokinetics

	Savaysa
Volume of distribution	107 L
Metabolism	Liver, minimal via hydrolysis, conjugation, and CYP3A4 oxidation; active M-4 metabolite
Excretion	Urine (50%), primarily unchanged
Half-life	10 to 14 hours
Protein binding	55%

In the Engage AF-TIMI 48 Trial assessing stroke and systemic embolism prevention, Savaysa™ was noninferior to warfarin in reducing the risk of stroke or systemic embolism in patients with nonvalvular atrial fibrillation.

STUDY DESIGN	Multinational, randomized, double-blind, double-dummy clinical trial (n=21,105).
INCLUSION CRITERIA	Patients 21 years and older with atrial fibrillation and an increased risk of stroke.
EXCLUSION CRITERIA	Patients with atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, other indications for anticoagulation, dual antiplatelet therapy, or at a high risk of bleeding.
TREATMENT REGIMEN	Patients were randomized to Savaysa 60 mg orally once daily, Savaysa 30 mg orally once daily, or warfarin (dose adjusted to a targeted INR range of 2 to 3).
RESULTS	After a median follow-up of 2.8 years, Savaysa was found to be noninferior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (yearly event rate, 1.18% (60-mg group) and 1.61% (30-mg group) vs 1.5%) but was not significantly superior to warfarin in efficacy. Savaysa was associated with significantly lower rates of major bleeding (yearly event rate, 2.75% in the 60-mg group vs 3.43% with warfarin), but did have a higher annualized rate of major gastrointestinal bleeding (yearly event rate, 1.51% in the 60-mg group vs 1.23% with warfarin). The rate of stroke or systemic embolism was lower with Savaysa 60 mg vs 30 mg.
SAFETY	The most common adverse reactions were related to bleeding. The incidence of major bleeding was 2.75%/year for Savaysa 60 mg compared with 3.43%/year for warfarin.

In the Hokusai-VTE Trial assessing DVT and PE treatment, Savaysa was noninferior to warfarin for recurrent VTE in patients with acute symptomatic VTE who were treated for 3 to 12 months following heparin or enoxaparin therapy for at least 5 days.

STUDY DESIGN	Multinational, randomized, double-blind, double-dummy clinical trial (n=8292).
INCLUSION CRITERIA	Adult patients with acute symptomatic DVT or PE (with or without DVT).
EXCLUSION CRITERIA	Patients who had received therapeutic heparin doses for > 48 hours, had received more than 1 dose of a vitamin K antagonist, had other indications

	for anticoagulation, or who continued treatment with aspirin or dual antiplatelet therapy.
TREATMENT REGIMEN	Initially, all patients received open-label Savaysa or unfractionated heparin for at least 5 days. Patients were randomized to receive Savaysa 60 mg orally once daily (starting after discontinuation of heparin) or warfarin (dose adjusted to a targeted INR range of 2 to 3; starting concurrently with heparin). Savaysa or warfarin treatment was to last for 3 to 12 months.
RESULTS	After 12 months of follow-up, Savaysa was found to be noninferior to warfarin for the primary endpoint of symptomatic recurrent VTE, defined as a composite of DVT or nonfatal or fatal PE (event rate, 3.2% vs 3.5%). In patients with a presenting diagnosis of pulmonary embolism, symptomatic VTE recurred in 2.8% with Savaysa and 3.9% with warfarin. Rates of major bleeding were similar between treatment groups (1.4% vs 1.6%), but there was a significantly lower rate of clinically relevant non-major bleeding in those treated with Savaysa (7.2% vs 8.9%).
SAFETY	The most common adverse reactions were related to bleeding. Overall, bleeding events occurred in 21.7% of Savaysa patients compared with 25.6% of warfarin patients.

Contraindications [(1)]

- Active pathological bleeding

Warnings and Precautions [(1)]

- Do not use in nonvalvular atrial fibrillation patients with CrCl > 95 mL/min due to reduced efficacy.
- Premature discontinuation increases the risk of ischemic events; if discontinued for reasons other than pathological bleeding or therapy completion, consider covering with alternative anticoagulant.
- Use caution in patients receiving neuraxial anesthesia or undergoing spinal puncture due to an increased risk of spinal or epidural hematoma, which may cause permanent paralysis; monitoring recommended; do not remove indwelling epidural or intrathecal catheters sooner than 12 hours after the last dose and wait 2 hours after catheter removal before administering.
- Mechanical heart valves or moderate to severe mitral stenosis; use not recommended.
- Serious and potentially fatal bleeding may occur.
- Moderate or severe hepatic impairment (Child-Pugh B or C); use not recommended.
- Renal impairment (CrCl 15 to 50 mL/min); dose adjustment necessary.
- Renal impairment (CrCl < 15 mL/min); use not recommended.
- Long-term use with other anticoagulants; not recommended.
- P-glycoprotein inducers (eg, rifampin); avoid use.
- Discontinue at least 24 hours prior to surgery if possible.

Adverse Effects [1]

ENGAGE AF-TIMI 48 Trial

Bleeding Events	Savaysa™ %/year (n=5417)	Warfarin %/year (n=5485)
Clinically relevant, non-major bleeding	9.4%	10.9%
Major bleeding	3.1%	3.7%
Gastrointestinal bleeding	1.8%	1.3%
Intracranial hemorrhage	0.5%	1%
Fatal bleeding	0.2%	0.4%

HOKUSAI VTE Trial

Bleeding Events	Savaysa™ (n=4118)	Warfarin (n=4122)
Clinically relevant, non-major bleeding	7.2%	8.9%
Major bleeding	1.4%	1.6%
Decrease in Hb ≥ 2 g/dL	1%	0.8%
Transfusion ≥ 2 units	0.7%	0.5%
Intracranial bleeding	0.1%	0.4%
Fatal bleeding	< 0.1%	0.2%

Drug Interactions [1]

- Anticoagulants
- Antiplatelets: aspirin, NSAIDs
- P-gp inducers: rifampin
- Thrombolytics

Dosage and Administration [1]

The recommended dose is 60 mg orally once daily. Depending on the indication, the dose may need to be reduced in patients with renal impairment, patients who weigh 60 kg or less, or patients taking certain concomitant P-gp inhibitors.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Edoxaban	Savaysa	Daiichi Sankyo	30 mg tabs	1 tablet daily	$332.64
			60 mg tabs	1 tablet daily	$332.64
Apixaban	Eliquis	Bristol-Myers Squibb	2.5 mg tabs	1 tablet twice daily	$303.08
			5 mg tabs	1 tablet twice daily	$303.08
Dabigatran	Pradaxa	Boehringer Ingelheim	75 mg caps	1 capsule twice daily	$272.53
			150 mg caps	1 capsule twice daily	$272.53
Rivaroxaban	Xarelto	Janssen	15 mg tabs	1 tablet daily	$292.21
			20 mg tabs	1 tablet daily	$292.21

*Wholesale Acquisition Cost

Conclusion

Savaysa™ is an oral, once daily factor Xa inhibitor anticoagulant indicated for the prophylaxis of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of DVT and PE after 5 to 10 days of initial therapy with a parenteral anticoagulant. The approval of Savaysa was based upon two multinational, randomized, double-blind clinical trials. In the ENGAGE AF-TIMI 48 trial in 21,105 patients with nonvalvular atrial fibrillation, Savaysa was noninferior to warfarin in reducing the risk of stroke and systemic embolism (yearly event rate, 1.18% vs 1.5%). Although it was associated with a significantly lower rate of major bleeding (yearly event rate, 2.75% vs 3.43%) compared with warfarin, it did have a higher annualized rate of major gastrointestinal bleeding (yearly event rate, 1.51% vs 1.23%). In patients with nonvalvular atrial fibrillation, Savaysa should not be used in patients with a CrCl > 95 mL/min due to reduced efficacy in preventing ischemic strokes. In the Hokusai-VTE trial of 8292 patients with acute symptomatic VTE, Savaysa was noninferior to warfarin for symptomatic recurrent VTE (event rate, 3.2% vs 3.5%) with a significantly lower rate of clinically relevant non-major bleeding (7.2% vs 8.9%) compared with warfarin. No routine blood testing is necessary with Savaysa, and no treatment is available to reverse its anticoagulant effect. The most common non-bleeding adverse events are rash and abnormal liver function tests.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Savaysa™, edoxaban tablets. Daiichi Sankyo, Inc, Parsippany, NJ, 01/2015.
2. Giugliano RP, Ruff CT, Braunwald E et al: Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369(22):2093-2104.
3. Hokusai-VTE Investigators, Buller HR, Decousus H et al: Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369(15):1406-1415.
4. Savaysa: A New Once-Daily Treatment. Retrieved June 2, 2015 from http://www.savaysa.com
5. Cardiology Patient Page: Pulmonary Embolism and Deep Vein Thrombosis. Retrieved June 2, 2015 from http://circ.ahajournals.org/content/106/12/1436.full

Prepared by: Luke Boehmer, PharmD

Date: June 2, 2015

