PDL NEW DRUG REVIEW

Proprietary Name: Savaysa®
Common Name: edoxaban
PDL Category: Anticoagulants

Comparable Products	Preferred Drug List Status
Eliquis	Non-Preferred with Conditions
Warfain	Preferred
Xarelto	Preferred with Conditions

Summary

Indications and Usage: To reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF) AND for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant. A limitation of use for the NVAF indication includes that it should not be used in patients with CrCl >95ml/min because of an increased risk of ischemic stroke as compared to warfarin.

This is a pregnancy category C medication. The safety and efficacy of use in children have not been established. Additionally, use is not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis.

Dosage Forms: Film-coated tablets: 15mg, 30mg, and 60mg

Recommended Dosage: *With NVAF*: Creatine clearance (CrCl) should be assessed prior to starting treatment and should not be initiated/used in those with CrCl >95ml/min. The recommended dose is 60mg QD. This does should be reduced to 30mg QD if CrCl is 15-50ml/min. *With DVT/PE:* Take 60mg QD, following 5-10 days of initial therapy with a parenteral anticoagulant. The recommended dose is 30mg QD with CrCl 15-50ml/min, in patients who weigh ≤60kg, or in patients who are taking certain concomitant P-gp inhibitor medications.

Savaysa® should be discontinued ≥24 hours before invasive or surgical procedures due to the risk of bleeding. Treatment can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established, but noting that the time to onset of pharmacodynamic effects is 1-2 hours. Use a parenteral anticoagulant and then switch to oral Savaysa® if oral medications cannot be taken during or after surgical intervention.

Please refer to the prescribing information for additional information regarding transitioning to or from other anticoagulant products. In addition, long-term concomitant treatment with Savaysa® and other anticoagulants is not recommended due to an increased risk of bleeding; however, short-term concomitant use may be needed for those transitioning to or from Savaysa®.

Dose adjustments are not required with mild hepatic impairment; however, the use of Savaysa® is not recommended in those with moderate or severe hepatic impairment. With renal impairment, reduce the dose of Savaysa® to 30mg QD with CrCl 15-50ml/min. Use is not recommended in those with CrCl <15ml/min.

The concomitant use of Savaysa® with rifampin should be avoided.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Savaysa®) minus reported % incidence for warfarin for NVAF patients with CrCl ≤95ml/min in the ENGAGE AF-TIMI 48 study. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than warfarin.* The most frequently reported adverse event included bleeding and was the most common reason for treatment discontinuation (3.9% vs 4.1% in the Savaysa® 60mg vs warfarin groups). In the overall population, major bleeding was lower in the Savaysa® group vs warfarin (3.1% vs 3.7%; hazard ratio [HR] 0.80).

The following table, which was adapted from the PI, illustrates the adjudicated bleeding events for NVAF patients with CrCl ≤95ml/min.

Event	Savaysa® 60mg (N=5417)	Warfarin (N=5485)	Hazard ratio (HR) For Savaysa® vs warfarin
Major bleeding	3.1%	3.7%	0.84
Intracranial hemorrhage (ICH)	0.5%	1%	0.44
Hemorrhagic stroke	0.3%	0.6%	0.49
Other ICH	0.2%	0.5%	0.37
Gastrointestinal	1.8%	1.3%	1.40
Fatal Bleeding	0.2%	0.4%	0.51
ICH	0.2%	0.3%	0.54
Non-intracranial	<0.1%	<0.1%	-
Clinically Relevant Non-Major Bleeding (CRNMB)	9.4%	10.9%	0.87

The most common non-bleeding adverse reactions for Savaysa® 60mg vs warfarin were rash (4.2% vs 4.1%) and abnormal liver function tests (4.8% vs 4.6%).

Contraindications: In those with active pathological bleeding

Manufacturer: Daiichi Sankyo Co, LTD

Analysis: Edoxaban, the active ingredient of Savaysa®, is a selective factor Xa inhibitor that does not need antithrombin III for antithrombotic activity. It inhibits free factor Xa, and prothrombinase activity and inhibits thrombin-induced platelet aggregation. Thus, Savaysa® reduces thrombin generation and thrombus formation.

Savaysa® has a box warning that includes the following: reduced efficacy in NVAF patients with CrCl>95ml/min; premature discontinuation of Savaysa® increases the risk of ischemic events; and spinal/epidural hematoma. In the ENGAGE AF-TIMI 48 study, NVAF patients with CrCl >95ml/min had an increased rate of ischemic stroke with Savaysa® 60mg vs warfarin treatment. Therefore it is recommended that this population use another anticoagulant. The premature discontinuation of any oral anticoagulant without adequate alternative anticoagulation increases the risk of ischemic stroke. If Savaysa® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant. Last, epidural or spinal hematomas may occur in those treated with Savaysa® who are receiving neuraxial anesthesia or undergoing spinal puncture, which may result in long-term or permanent paralysis. These risks should be considered when scheduling for spinal procedures.

There were 2 major studies performed to assess the safety and efficacy of edoxaban, the ENGAGE AF-TIMI 48 and the Hokusai VTE study.

ENGAGE AF-TIMI 48 study: This was a 48 week, double-blind, non-inferiority study to assess the safety and efficacy of edoxaban as compared with warfarin for reducing the risk of stroke and systemic embolic events in patients with NVAF (N=21,105). Inclusion criteria included adults with a prior stroke, TIA, or non-CNS systemic embolism OR ≥2 of the following risk factors: age ≥75 years, hypertension, heart failure, or DM. The primary endpoint was the occurrence of first stroke (either ischemic or hemorrhagic) or of a systemic embolic event (SEE) that occurred during treatment or within 3 days from the last dose taken; the main safety endpoint was major bleeding.

Note that the modified intent-to-treat (mITT) population included patients who underwent randomization and received ≥1 one dose of the study drug during the treatment period. The ITT population was included in the prespecified superiority analysis with data from the overall study period. Results suggested that edoxaban was non-inferior to warfarin. As non-inferiority was met, superiority was tested. In the ITT population, superiority was not seen.

With regards to the safety endpoints, there were fewer bleeding events with edoxaban 60mg vs warfarin with one exception of GI bleeding. The bleeding events that were significantly lower with edoxaban 60mg vs warfarin included: major bleeding, fatal, any intracranial bleed, fatal intracranial bleed, life-threatening bleed, clinically relevant non-major bleeding (CRNMB), minor bleeding, major or clinically relevant non-major bleeding, and any overt bleeding. GI bleeding occurred significantly more with edoxaban 60mg than warfarin. The table below, which was adapted from the PI, illustrates efficacy and some safety results.

Event	Savaysa® 30mg (N=7002)	Savaysa® 60mg (N=7012)	warfarin (N=7012)	Hazard ratio (HR) S®30 vs warfarin	Hazard ratio (HR) S®60 vs warfarin
Efficacy endpoints (rates were %/year)					
First stroke or SEE (mITT)	1.6%	1.2%	1.5%	1.07 (p=0.44*)	0.79 (p=0.017)
First stroke or SEE (ITT)	2.04%	1.57%	1.8%	1.13 (p=0.10*)	0.87 (p=0.08*)
Hemorrhagic stroke	0.16%	0.26%	0.47%	0.33 (p<0.001*)	0.54 (p <0.001*)
Ischemic stroke	1.77%	1.25%	1.25%	1.41 (p<0.001*)	1 (p=0.97*)
Safety endpoints					
Major bleeding	1.61%	2.75%	3.43%	0.47 (p<0.001)	0.80 (p<0.001)
GI bleeding	0.82%	1.51%	1.23%	0.67 (p<0.001)	1.23 (p<0.03)
CRNMB	6.6%	8.67%	10.15%	0.66 (p<0.001)	0.86 (p<0.001)

* Savaysa® was non-inferior to warfarin. These P-values are those representing the superiority analysis.

Hokusai VTE study: This was a double-blind non-inferiority study to assess the safety and efficacy of edoxaban 60mg (or 30mg if met criteria for this dose) as compared with warfarin in patients (N=8240) with acute venous thromboembolism (VTE; DVT or PE with or without DVT) who had initially received heparin or enoxaparin for ≥5 days. The primary outcome was symptomatic VTE, defined as the composite of recurrent DVT, new non-fatal symptomatic PE, or fatal PE during the 12 month study period; the primary safety outcome was clinically relevant bleeding, defined as the composite of major or clinically relevant non-major bleeding (CRNMB). Analysis was performed with the modified intent-to-treat (mITT) population, which included those who received at least one dose of the study drug.

Results suggested that edoxaban was non-inferior to warfarin for the primary efficacy outcome; however, some safety bleeding events were significantly different. The following table illustrates results of this study.

Event	Savaysa® (N=4118)	warfarin (N=4122)	Hazard ratio (HR) S® vs warfarin
Efficacy Endpoints			
Symptomatic recurrent VTE	3.2%	3.5%	0.89
Safety Endpoints			
Clinically relevant bleeding	8.5%	10.3%	0.81 (p=0.004)

Event	Savaysa® (N=4118)	warfarin (N=4122)	Hazard ratio (HR) S® vs warfarin
Major bleeding	1.4%	1.6%	0.84 (p=0.35)
CRNMB	7.2%	8.9%	0.80 (p=0.004)
Any bleeding	21.7%	25.6%	0.82 (p<0.001)

Numerous network, indirect met-analyses are available that assess the safety and efficacy of edoxaban as compared with other agents within the same therapeutic drug class.

A 2014 systematic review and indirect treatment comparison meta-analysis by Kang et al[4] included 6 randomized trials (N=27,069) to assess the safety and efficacy of NOACs (new oral anticoagulants) for the treatment of acute VTE. The NOACs included rivaroxaban, dabigatran, apixaban, and edoxaban, with parenteral anticoagulant/oral vitamin K antagonists (VKA) being the common comparator. The efficacy outcomes assessed included mortality, recurrent symptomatic VTE, recurrent DVT, and current PE. Results suggested that there were no significant differences among all of the comparisons made for the efficacy outcomes. In regards to bleeding, the risk of major bleeding increased with dabigatran vs apixaban (relative risk [RR] 2.69) and with edoxaban vs apixaban (RR 2.74).

A 2014 indirect comparison meta-analysis by Mantha et al[5] included 6 randomized trials (N=27,069) to assess the safety and efficacy of the four NOACs when used for the treatment of acute VTE. The NOACs included rivaroxaban (RIV), dabigatran (DAB), apixaban (APIX), and edoxaban (EDOX). The primary outcome assessed was recurrent VTE, while a secondary endpoint included mortality. The primary safety endpoint was the occurrence of major bleeding, while a secondary safety endpoint was the composite of major or clinically relevant non-major bleeding.

Results suggested that there were not statistically significant differences in the risk of recurrent VTE or all-cause mortality between the 4 treatments. In regards to major bleeding, there were differences seen which included the following: APIX vs DAB (RR 0.42; p=0.02) compared with APIX vs RIV (RR 0.57; p=0.12), APIX vs EDOX (RR 0.37; p<0.001), RIV vs DAB (RR 0.74; p=0.30), RIV vs EDOX (0.64; p=0.10), and EDOX vs DAB (RR 1.15; p=0.62). For the composite of major or clinically relevant non-major bleeding, differences seen were as follows: APIX vs DAB (RR 0.71; p=0.02), APIX vs RIV (RR 0.47; p<0.001), APIX vs EDOX (RR 0.54; p<0.001), RIV vs DAB (RR 1.50; p=0.001), RIV vs EDOX (RR 1.15; p=0.16), and EDOX vs DAB (RR 1.31; p=0.04). The authors concluded that while there was not a significant difference in efficacy between the four treatments, apixaban was associated with a lower risk of bleeding.

A 2014 meta-analysis by Providencia et al[6] included 7 phase III randomized, controlled trials (N=80,290) to assess the safety and efficacy of direct thrombin inhibitors (DTI) and factor Xa Inhibitors (FXaI) as compared with warfarin in patients being treated for afib. Different dosing regimens (e.g. QD or BID) were also assessed. When the DTIs and FXa1 were pooled, these NOACs were associated with a lower incidence of stroke or systemic embolism (SE, RR 0.84; p=0.006) and major bleeding (RR 0.79; p=0.004) as compared with warfarin. In addition, results also favored NOACs vs warfarin for total mortality (RR 0.90; p<0.0001), cardiovascular mortality (RR 0.88; p=0.0002), and intracranial bleed (RR 0.49; p<0.00001). Significant differences between treatments were not seen, however, with ischemic stroke, MI, and GI bleed. Significant differences were not seen between once-daily and twice-daily regimens. Warfarin was more effective than some NOACs for some secondary endpoints, including edoxaban 30mg for ischemic stroke, dabigatran for acute MI, and dabigatran 150mg and rivaroxaban 20mg with regards to GI bleed. The authors concluded that "...the choice of NOAC should be adapted to the specific patient and focused on the agent itself, rather than the pharmacological class or dosing regimens."

A 2014 meta-analysis by Li et al[7] included five randomized controlled trials (N=31,262) to assess the safety of edoxaban as compared with warfarin. Outcomes assessed included bleeding risk and mortality. Results of the pooled data suggested that edoxaban was associated with a decrease in major or clinically relevant non-major bleeding (CRNMB) as compared with warfarin (risk ratio [RR0 0.78; p<0.001) and any bleeding events (RR 0.82;

p<0.001). Furthermore, edoxaban was also associated with a decrease in any major bleeding (RR 0.67; p<0.001), CRNMB (RR 0.79; p<0.001), minor bleeding (RR 1.04; p=0.35), and fatal bleeding (RR 0.42; p<0.001). Of the 5 studies, only 2 reported on all-cause death and 3 reported events of CV deaths. Results suggested that edoxaban was also superior to warfarin in the reduction rates of all-cause death (RR 0.92; p=0.02) and CV death (RR 0.87; p=0.004). The authors concluded that edoxaban demonstrated a favorable safety profile in regards to bleeding and mortality as compared to warfarin; however, further randomized controlled trials are needed to confirm these results.

Numerous indirect meta-analyses are available, and data seems to suggest that statistically significant differences are not seen between edoxaban (Savaysa®) and other currently available newer oral anticoagulants. While numerical differences in certain safety endpoints of bleeding rates have been shown, this has not been proven in direct head-to-head studies. In conclusion, there is no data found to suggest that Savaysa® is safer or more effective than the other novel oral anticoagulant (NOACs) medications available within the class. As with other NOACs, evidence is found to suggest lower rates of most types of bleeding than occur with warfarin, but a disadvantage is the lack of an agent that can reverse the anticoagulant effects. The latest version of the AHA/ASA guidelines continues to recommend either warfarin or the NOACs for the prevention of strokes in patients with non-valvular atrial fibrillation.[8] It is recommended that Savaysa® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

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[7] Li S, Liu B, Xu D, et al. Bleeding risk and mortality of edoxaban: a pooled meta-analysis of randomized controlled trials. *PLoS One*. 2014; 9(4):e95354.
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