Edoxaban (SAVAYSA)
National Drug Monograph
October 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action[1]	Edoxaban is the fourth approved target specific oral anticoagulant (TSOAC) and the third approved selective oral factor Xa inhibitor available in the United States. Through inhibition of factor Xa, edoxaban reduces thrombin generation and thrombus formation.
Indication(s) Under Review in this document	**FDA Approved Indications:** • To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF); Note: The review focuses on the high dose of edoxaban (60 mg or 30 mg dose reduced) since it was the only dose approved by FDA. • To treat deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with an injectable anticoagulant
Dosage Form(s) Under Review[1]	60 mg, 30 mg, and 15 mg oral tablets
REMS[1]	No REMS
Pregnancy[1]	Pregnancy Category C. *See Special Populations for additional information*

Executive Summary	
Efficacy[1,2]	• For the treatment of NVAF, results from ENGAGE AF-TIMI 48 showed that the FDA approved high dose edoxaban (60 mg daily or dose reduced to 30 mg daily) was noninferior to adjusted dose warfarin for the reduction of the primary composite endpoint of stroke (ischemic or hemorrhagic) or systemic embolic event (1.18% per year vs. 1.50% per year, respectively; HR 0.79; 95% CI 0.63 – 0.99; p <0.001 for noninferiority). Edoxaban was associated with a significant reduction in hemorrhagic stroke compared to warfarin but not in ischemic stroke or systemic embolic events. • For the treatment of venous thromboembolic events (VTE) (DVT and PE), results from HOKUSAI-VTE showed that edoxaban was noninferior to adjusted dose warfarin for the reduction of recurrent, symptomatic VTE in patients treated up to 12 months.
Safety	• Bleeding is the main concern with edoxaban. • In a NVAF population exposed to study drug for a median of 2.5 years, the FDA approved high dose of edoxaban (60 mg or 30 mg dose reduced) was associated with less International Society of Thrombosis and Haemostasis (ISTH) major bleeding compared to warfarin in the ENGAGE AF trial (2.8% vs. 3.4% annually; HR 0.80; 95% CI 0.71-0.91). Except for an excess of gastrointestinal (GI) bleeding, high dose edoxaban was associated with less bleeding overall compared to warfarin for all other bleeding endpoints evaluated. • In a VTE population where patients were treated for up to 12 months, edoxaban

	was associated with significantly less clinically relevant bleeding (includes major plus nonmajor clinically relevant bleeding) (8.5% vs. 10.3%; HR 0.81; 95% CI 0.71 – 0.94) compared to warfarin. There was an excess of vaginal and GI bleeding in the edoxaban vs. warfarin groups, but other bleeding endpoints favored edoxaban.
	• **Boxed warning:**
	  o Reduced efficacy in NVAF patients with creatinine clearance (CrCl) >95 ml/min
	  o Premature discontinuation of edoxaban increases risk of ischemic events
	  o Spinal/epidural hematoma risk
	• **Other warnings:**
	  o Mechanical heart valves or moderate to severe mitral stenosis

Potential Impact	• Edoxaban is the fourth TSOAC approved in the U.S. **NVAF:** • High dose (60 mg or reduced to 30 mg daily) edoxaban was noninferior to adjusted dose warfarin for the reduction in all cause stroke and systemic embolism; however, due to a finding of reduced efficacy in patients with good renal function, FDA labeling states that edoxaban should not be used in patients with a CrCl >95 ml/min. • Except for an increase in GI bleeding, high dose edoxaban was associated with less bleeding compared to warfarin. • Efficacy and safety of edoxaban appear to be maintained in the elderly population. Edoxaban is partially eliminated by the kidneys. A reduced dose for patients with renal impairment is available and has been clinically studied. **VTE Treatment:** • Edoxaban was noninferior to adjusted dose warfarin for the reduction of recurrent VTE without limitations based on renal function. • Though edoxaban was associated with less clinically relevant bleeding compared to warfarin, an excess of GI bleeds and vaginal bleeds were found. • A reduced dose of edoxaban for the VTE indication is FDA approved and was studied clinically for patients with renal impairment, low body weight, or who are taking certain P-glycoprotein inhibitors. In the pivotal HOKUSAI VTE trial, edoxaban was started after initial treatment with an injectable anticoagulant. **Patient convenience:** • Edoxaban offers a once daily regimen. Compared to warfarin, edoxaban requires less frequent laboratory monitoring and has no dietary restrictions. Tolerability of edoxaban and warfarin were comparable in clinical trials.

Background

Purpose for review	Recent FDA approval Issues to be determined: ✔ Does edoxaban offer advantages to currently available alternatives? ✔ Does edoxaban offer advantages over current VANF agents? ✔ What safety issues need to be considered? ✔ Does edoxaban have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?
Other therapeutic options	• Edoxaban is the fourth TSOAC approved in the U.S. All currently available TSOACs have been compared to warfarin for the NVAF and VTE treatment indications in large, randomized controlled trials (RCTs). There are no head-to- head RCTs comparing TSOACs. • All options discussed below are on VA National Formulary (VANF).

- For NVAF, warfarin and TSOACs are considered appropriate first-line options. The TSOACs are restricted to Criteria for Use (CFU). Dabigatran is the preferred TSOAC in VA; rivaroxaban and apixaban are available when compelling indications for an alternative to dabigatran exist.
- For VTE treatment, warfarin and TSOACs are considered appropriate first-line options. The TSOACs are restricted to CFU, and there is no preferred TSOAC for the VTE treatment indication.

VANF options for NVAF and VTE Indications

Drug	Dosing	Efficacy vs. warfarin	Major bleed vs. warfarin	Other Considerations
Warfarin	daily	NVAF		• Need for individualized dosing and frequent INR monitoring • Multiple drug-drug, -disease, -diet interactions
		Well established standard	Well established standard	
		VTE		
		Well established standard	Well established standard	
Dabigatran	BID	NVAF		• Storage limitations • Increased GI bleeding vs. warfarin • Primarily renal elimination • Reduced dose not clinically studied (NVAF)
		Superior	Similar	
		VTE		
		Noninferior	Similar	
Rivaroxaban	daily	NVAF		• Must take with meal for adequate absorption • Increased GI bleeding vs. warfarin (NVAF)
		Noninferior	Similar	
		VTE		
		Noninferior	Similar/ Superior	
Apixaban	BID	NVAF		• None
		Superior	Superior	
		VTE		
		Noninferior	Superior	
Aspirin plus clopidogrel	daily	NVAF		• Limited use; should only be considered in patients who cannot receive any other anticoagulant
		Inferior	Similar	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms <edoxaban> and <Savaysa>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All relevant randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

- FDA approval of edoxaban for the treatment of NVAF was based on the pivotal Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF-TIMI 48) trial. Results showed that high dose edoxaban was noninferior to adjusted dose warfarin for the primary composite endpoint of stroke (ischemic or hemorrhagic) or systemic embolic event. There was a significant reduction in the individual component of hemorrhagic stroke compared to warfarin, but not in the ischemic stroke or systemic embolic event endpoints.
- FDA approval of edoxaban for the treatment of VTE was based on the pivotal HOKUSAI-VTE trial. Results from HOKUSAI showed that edoxaban was noninferior to adjusted dose warfarin for the reduction of recurrent, symptomatic VTE over a period of up to 12 months' treatment duration.

- Overall, there is moderate quality evidence on the use of edoxaban for the reduction of stroke and systemic embolism in patients with NVAF and for the reduction in the risk of recurrent, symptomatic VTE in patients with acute VTE (see Appendix A).

ENGAGE-AF TIMI 48[2]

- ENGAGE-AF TIMI 48 was a phase 3, multicenter, multinational, randomized, double-blind, double-dummy, non-inferiority, industry sponsored trial that compared two doses of edoxaban ("high dose" of 60 mg or "low dose" of 30 mg once daily) to adjusted dose warfarin (INR goal 2-3) in patients with NVAF and a $CHADS_2$ score of 2 or higher. Edoxaban doses were halved (60 mg to 30 mg and 30 mg to 15 mg) if patients had any of the following: CrCl 30-50 ml/min, body weight of ≤60 kg, or concomitant use of verapamil or quinidine (or dronedarone after protocol amendment).
- Key exclusion criteria: AF due to a reversible cause; CrCl <30 ml/min; high bleeding risk; dual antiplatelet therapy; moderate-to-severe mitral stenosis or mechanical heart valve; additional indication for anticoagulation therapy; acute coronary syndrome, coronary revascularization, or stroke within 30 days before randomization.
- A total of 21,105 patients were randomized to treatment and followed for a median of 2.8 years. The study population was 62% male and well balanced between treatment groups, with a median age of 72 years, mean $CHADS_2$ score of 2.8, and a mean time in therapeutic range (TTR) of 65%. About 40% of the patients were 75 years or older, 28% had a history of stroke or transient ischemic attack (TIA), 41% were vitamin K antagonist naïve, and roughly 30% of patients were receiving aspirin at baseline. One quarter of the edoxaban patients were dosed reduced at baseline, most often due to low CrCl +/- other factors.
- For the primary composite efficacy endpoint of stroke (ischemic or hemorrhagic) or systemic embolic event, high dose edoxaban (60 mg or 30 mg dose adjusted), the dose approved by the FDA, was noninferior to warfarin in the modified intention to treat population (See table below). High dose edoxaban failed to achieve statistical superiority compared to warfarin in the prespecified superiority analysis (calculated in the intent-to-treat population). Since the efficacy endpoints were tested in a hierarchical design, once one test criterion was not satisfied, other secondary endpoints tested below that level were considered hypothesis generating.[3] Looking at type of stroke, high dose edoxaban was associated with fewer hemorrhagic strokes but no difference in ischemic stroke. There was a numerical reduction in cardiovascular mortality with high dose edoxaban vs. warfarin and a favorable trend in all-cause mortality. Hazard ratios for other efficacy endpoints and key secondary composite endpoints were all favorable for high dose edoxaban vs. warfarin. Low dose edoxaban (30 mg or 15 mg dose adjusted) was also deemed noninferior to warfarin, though this dose trended worse than warfarin for many of the efficacy endpoints and is not FDA approved as full dose treatment for NVAF.

ENGAGE-AF TIMI 48 Selected Efficacy Endpoints Overall Study Population[2]

Outcome	High-Dose EDOX n=7035	Warfarin n=7036	HR (95%CI)	P value
	Number (annual %)			
Primary Composite Endpoint				
Modified ITT treatment period†	182 (1.18)	232 (1.50)	0.79 (0.63-0.99)	<0.001
ITT overall study period§	296 (1.57)	337 (1.80)	0.87 (0.73-1.04)	0.08
Stroke				
Ischemic	236 (1.25)	235 (1.25)	1.00 (0.83-1.19)	0.97
Hemorrhagic	49 (0.26)	90 (0.47)	0.54 (0.38-0.77)	<0.001
Systemic Embolic Event	15 (0.08)	23 (0.12)	0.65 (0.34-1.24)	0.19
Death				
Any cause	773 (3.99)	839 (4.35)	0.92 (0.83-1.01)	0.08
Cardiovascular	530 (2.74)	611 (3.17)	0.86 (0.77-0.97)	0.013
Myocardial infarction	133 (0.70)	141 (0.75)	0.94 (0.74-1.19)	0.60

Primary composite endpoint = stroke (ischemic or hemorrhagic) or systemic embolic event; CI=confidence interval; HR=hazard ratio; ITT=intention to treat;
†For noninferiority testing
§For superiority testing

- Subgroup analysis showed overall consistency with the treatment effect of high dose edoxaban vs. warfarin, including those younger than 75 and 75 and older. A statistically significant interaction between treatment and subgroup was identified in patients with and without prior VKA treatment.

- In contrast to overall study results, when efficacy outcomes were examined by baseline renal function, patients with "normal" renal function (CrCl >80 ml/min) who received high dose edoxaban tended to do worse than warfarin for the primary composite endpoint and for the individual endpoint of ischemic stroke. Further, the negative trend became statistically significant in patients with CrCl >95 ml/min who received high dose edoxaban vs. warfarin. For patients with mild renal impairment (CrCl >50 to ≤80 ml/min), rates of ischemic stroke were lower for high dose edoxaban vs. warfarin. Pharmacokinetic and pharmacodynamic data support lower drug exposure and bleeding rates with edoxaban in patients with CrCl >95 ml/min compared to patients with CrCl ≤95 ml/min. As a result, FDA recommendations for approval of edoxaban include that the drug not be used in patients with a CrCl >95 ml/min for NVAF.[1]

HOKUSAI-VTE[4]

- HOKUSAI-VTE was a phase 3, multicenter, multinational, randomized, double-blind, double-dummy, non-inferiority, industry sponsored trial that compared edoxaban 60 mg daily and adjusted dose warfarin (International Normalized Ratio [INR] goal 2-3), in patients with acute, symptomatic VTE for at least 3 months and up to 12 months, as determined by the investigator. All patients were followed for 12 months, regardless of study drug treatment duration. All patients received initial therapy with an injectable anticoagulant (unfractionated heparin or enoxaparin) for at least 5 days and until INR was therapeutic. The edoxaban dose was reduced to 30 mg daily in patients with CrCl 30-50 ml/min, body weight of ≤60 kg, or who were receiving concomitant therapy with certain potent P-glycoprotein (P-gp) inhibitor (see Drug Interaction section for additional details).
- Key exclusion criteria: thrombectomy, caval filter insertion, fibrinolytics, significant liver disease, cancer with anticipated long term low molecular weight heparin treatment, another indication for anticoagulation therapy, CrCl <30 ml/min, active bleeding or high risk of bleeding where anticoagulant is contraindicated, aspirin >100 mg daily, dual antiplatelet therapy, chronic nonsteroidal anti-inflammatory drugs (NSAID) use, concomitant use of certain potent P-gp inhibitors (see Dose and Administration section for details).
- A total of 8,292 patients were randomized to treatment and followed for 12 months. About 40% of patients received active treatment for the 12 months' duration, and about 18% received the reduced dose of edoxaban at randomization. The study population was comprised of 57% males and had a mean age of 56 years (13% were 75 years or older). The majority of the population was Caucasian with few Black or African American patients. The average TTR was 63.5%. Of the 40% of patients with PE, about one third also had right ventricular dysfunction. Initial injectable anticoagulants were used for a median of 7 days, and the majority of qualifying VTE events were unprovoked.
- For the primary composite efficacy endpoint of adjudicated, symptomatic, recurrent VTE or VTE-related death, edoxaban was noninferior (but not superior) to adjusted dose warfarin. Event rates were similar between treatment groups among patients who presented with DVT both during the entire study period and the on-treatment period. In patients presenting with PE, event rates in both the whole study period and the on-treatment period favored edoxaban but the differences did not reach statistical significance. Primary event rates were similar in the full dose (60 mg) and reduced dose (30 mg) edoxaban groups compared to warfarin.[5]

HOKUSAI VTE Selected Efficacy Endpoints Overall Study Population

Outcome	Edoxaban n=4,118	Warfarin n=4,122	HR (95% CI)	P value*
	Number (%)			
Primary Composite Endpoint				
Event during overall study period	130 (3.2)	146 (3.5)	0.89 (0.70-1.13)	<0.001
Event during on-treatment period	66 (1.6)	80 (1.9)	0.82 (0.60-1.14)	<0.001
Patients with index DVT	n=2,468	n=2,453		
Event during overall study period	83 (3.4)	81 (3.3)	1.02 (0.75-1.38)	-
Event during on-treatment period	48 (1.9)	50 (2.0)	0.96 (0.64-1.42)	-
Patients with index PE	n=1650	n=1669		
Event during overall study period	47 (2.8)	65 (3.9)	0.73 (0.50-1.06)	-
Event during on-treatment period	18 (1.1)	30 (1.8)	0.60 (0.34-1.08)	-

Primary composite endpoint = recurrent VTE or VTE-related death; *P value for non-inferiority; CI=confidence interval; DVT=deep vein thrombosis; PE=pulmonary embolism

- Overall, similar treatment effects were observed among several subgroups evaluated, though there were trends of greater benefit of edoxaban vs. warfarin in patients 75 years of age and older compared to younger patients as well as in fragile patients compared to nonfragile patients.
- Unlike the FDA's recommendation against the use of edoxaban in patients with normal renal function for the treatment of NVAF, the FDA concluded that similar recommendations were not needed for the VTE treatment indication.[5]

Potential Off-Label Use

- **VTE prophylaxis:** Edoxaban has been studied in total knee replacement, total hip replacement, and hip fracture surgery in study populations from Japan and Taiwan.[6]

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning[1]	• **Reduced efficacy in NVAF patients with CrCl >95 ml/min** • **Premature discontinuation of edoxaban increases risk of ischemic events** • **Spinal/epidural hematoma** *(see Warnings/Precautions)*
Contraindications[1]	• Active pathological bleeding

Warnings/Precautions[1]	• **Reduced efficacy in NVAF in patients with CrCl >95 ml/min:** In the ENGAGE-TIMI 48 study, NVAF patients with CrCl >95 ml/min had an increased rate of ischemic stroke with edoxaban 60 mg daily compared to warfarin. An alternative anticoagulant should be chosen in these patients.
	• **Increased risk of stroke upon discontinuation of edoxaban in patients with NVAF:** Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If edoxaban is discontinued for reasons other than pathological bleeding or completed course of therapy, consider coverage with another anticoagulant.
	• **Risk of bleeding:** Edoxaban increases the risk of bleeding including fatal bleeding.
	  o Discontinue edoxaban in the setting of active pathological bleeding.
	  o Concomitant use of edoxaban with other drugs that affect hemostasis may increase the risk of bleeding (e.g., aspirin and other antiplatelet agents, antithrombotic agents, fibrinolytic therapy, and chronic use of NSAIDs.
	  o There is no specific reversal agent for edoxaban available. Edoxaban's effects are expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. Hemodialysis does not significantly contribute to edoxaban clearance. Other reversal agents such as protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of edoxaban.
	• **Risk of epidural or spinal hematoma:** Patients treated with antithrombotic agents and who are undergoing spinal/epidural anesthesia or puncture are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.
	  o The risk of events may be increased by postoperative use of indwelling catheters or concomitant use of medicines that affect hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of edoxaban. The next dose of edoxaban should not be administered earlier than 2 hours after the removal of the catheter. The risk may

also be increased by traumatic or repeated epidural or spinal puncture.
    - Monitor patients for signs and symptoms of neurological impairment. If neurological impairment is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, the potential benefits and risks in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis should be considered.
- **Mechanical heart valves or moderate to severe mitral stenosis:** Safety and efficacy of edoxaban has not been studied in these patients, and use is not recommended.
    - There were 321 patients included in the ENGAGE AF-TIMI 48 trial with a history of bioprosthetic valves or valve surgery. Further information on this patient population is unknown, though analysis and future publication is planned.[7]

Safety Considerations[1,2,3,4]

The clinical safety for edoxaban is based primarily on data from the ENGAGE AF-TIMI 48 and HOKUSAI VTE studies, including over 11,000 patients exposed to edoxaban 60 mg daily and 7,000 patients exposed to edoxaban 30 mg daily.

- The main concern with edoxaban is bleeding.
- In the treatment of NVAF, patients from the ENGAGE AF trial were exposed to study drug for a median of 2.5 years. In the total study population, high dose edoxaban (60 mg or 30 mg dose reduced) was associated with less ISTH major bleeding compared to warfarin. When examined by the subgroup of patients with a CrCl ≤95 ml/min (the FDA approved population), the benefit of edoxaban over warfarin remained. Except for an excess of GI bleeding, high dose edoxaban was associated with less bleeding overall compared to warfarin for all other bleeding endpoints evaluated. Lower bleeding rates with high dose edoxaban vs. warfarin were consistently observed across most subgroups including patients 75 years and older and younger patients; however, the reduction in bleeding with edoxaban was significantly greater in patients who received a dose adjustment at randomization vs. those who did not. There was also a trend of a greater reduction in bleeding with high dose edoxaban in patients with low center level TTR.

ENGAGE AF-TIMI 48: Selected Bleeding Endpoints Overall Study Population[2]

Bleeding Endpoint	High Dose EDOX n=7,012 annual %	Warfarin n=7,012 annual %	HR (95% CI)	P value (for superiority)
Major*	2.8	3.4	0.80 (0.71-0.91)	<0.001
Fatal	0.2	0.4	0.55 (0.36-0.84)	0.006
Any intracranial	0.4	0.9	0.47 (0.34 – 0.63)	<0.001
Gastrointestinal	1.5	1.2	1.23 (1.02 – 1.50)	0.03
Life threatening	0.4	0.8	0.51 (0.38 – 0.70)	<0.001
Major or clinically relevant nonmajor	11.1	13.0	0.86 (0.80-0.92)	<0.001

*ISTH Major bleeding=clinically overt bleeding that met one of the following criteria: fatal bleeding; symptomatic bleeding in a critical site such as retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome; fall in hemoglobin of ≥2 g/dL, when adjusted for transfusions. HR=hazard ratio; CI=confidence interval

- In the treatment of VTE, patients from the HOKUSAI VTE trial were treated for up to 12 months with edoxaban or adjusted dose warfarin. Edoxaban was associated with significantly less clinically relevant bleeding (includes major plus nonmajor clinically relevant bleeding) compared to warfarin. There was a trend of less major bleeding with edoxaban. The number of fatal and other critical bleeding events including intracranial bleeding was small but favored edoxaban as well. In contrast, there was an excess of GI and vaginal bleeding with edoxaban vs. warfarin. Results were consistent across many subgroups studied including patients younger than 75 and 75 and older and those with renal impairment, though the reduction in bleeding with edoxaban vs. warfarin in males was greater than females and in patients with a low center level TTR.

HOKUSAI VTE: Selected Bleeding Endpoints On Treatment[1,4]

Bleeding Endpoint	Edoxaban n=4,118 %	Warfarin n=4,122 %	HR (95% CI)	P value (for superiority)
Clinically relevant*	8.5	10.3	0.81 (0.71-0.94)	<0.004
Major†	1.4	1.6	0.84 (0.59-1.21)	0.35
Fatal	<0.1	0.2	-	-
Nonfatal intracranial	0.1	0.3	-	-
Clinically relevant nonmajor	7.2	8.9	0.80 (0.68-0.93)	0.004
Any	21.7	25.6	0.82 (0.75-0.90)	<0.001
Gastrointestinal	4.2	3.6	-	-
Vaginal	9.0	7.1	-	-

Bleeding events on treatment defined as time that patients were receiving study drug or within 3 days of stopping or interrupting; HR=hazard ratio; CI=confidence interval
*Clinically relevant bleeding was the primary safety endpoint and included major and clinically relevant nonmajor bleeds.
†Major bleeding=clinically overt bleeding that met one of the following criteria: fall in hemoglobin of ≥2g/dL; transfusion of ≥2 units of blood; occurring in a critical site or organ; contributing to death.

Adverse Reactions

Common adverse reactions	Bleeding is the main concern with edoxaban.
Death/Serious adverse reactions	**Deaths** • In the ENGAGE AF trial, there were 769 (11%) deaths in the high dose edoxaban group and 836 deaths (12%) in the warfarin group, with the majority in both groups being cardiovascular related.[9] • In the HOKUSAI VTE trial, there were 132 (3.2%) deaths in the edoxaban group and 126 (3.1%) deaths in the warfarin group. The excess deaths in the edoxaban group were cardiovascular or infectious disease related.[8] **Serious and Other Adverse Events** • In the ENGAGE AF trial, non-bleeding serious adverse events (SAEs) were reported with similar frequencies between both edoxaban groups and warfarin groups (36 to 38%). Overall, the type and frequency of events reported were similar between treatment groups; however, there were more anemia-related SAEs and an excess of interstitial lung disease (ILD)-related SAEs and ILD-related deaths with high dose edoxaban vs. warfarin (15 vs. 7 ILD-SAEs; 5 vs. 0 ILD-deaths).[1,9] • In the HOKUSAI VTE trial, SAEs were reported in 12.2% and 13.2% of patients receiving edoxaban and warfarin, respectively. There were 21 (0.5%) acute coronary events in the edoxaban group compared to 16 (0.3%) in the warfarin group.[4] • Per FDA review of all available safety data, it does not appear that edoxaban causes drug-induced liver injury.[9]
Discontinuations due to adverse reactions	• Bleeding was the most common reason for treatment discontinuation in clinical trials. • ENGAGE AF: o Due to bleeding:[1] high dose edoxaban 3.9% (vs. 4.1% with warfarin) o Non-bleeding:[3] high dose edoxaban 5.3% (vs. 4.0% with warfarin) • HOKUSAI VTE: o Due to bleeding:[1] edoxaban 1.4% (vs. 1.4% with warfarin) o Non-bleeding:[4] edoxaban 1.0% (vs. 1.2% with warfarin)

Drug Interactions

Drug-Drug Interactions[1]
Edoxaban is a substrate of P-gp transporter. Concomitant use of edoxaban and P-gp inhibitors may potentially increase edoxaban exposure; use of edoxaban and P-gp inducers may decrease edoxaban exposure.

- **P-gp inducers:** Avoid concomitant use of edoxaban and rifampin.
- **P-gp inhibitors:**
  - For NVAF, no dose adjustments of edoxaban are recommended with concomitant use of P-gp inhibitors based on clinical data from the ENGAGE AF study (Dose reductions studied in patients receiving concomitant P-gp inhibitors resulted in lower edoxaban levels than in patients given full dose).
  - For VTE, a reduced dose of edoxaban of 30 mg daily is recommended for patients receiving certain potent P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or ketoconazole) based on clinical data from the HOKUSAI VTE trial. Use of other P-gp inhibitors including protease inhibitors (ritonavir, nelfinavir, indinavir, saquinavir) and cyclosporine was not allowed.

Drug-Food Interactions[1] None known.

Drug-Lab Interactions[1]
Edoxaban prolongs clotting time tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT); however, changes in PT, INR, and aPTT are variable and not useful in monitoring the anticoagulant effect of edoxaban.

Risk Evaluation

As of September 24, 2015

<table>
<tr><th></th><th>Comments</th></tr>
<tr><td>Sentinel event advisories</td><td>• None
• Sources: ISMP, FDA, TJC</td></tr>
<tr><td>Look-alike/sound-alike error potentials</td><td>
<table>
<tr><th>NME Drug Name</th><th>Lexi-Comp</th><th>First DataBank</th><th>ISMP</th><th>Clinical Judgment</th></tr>
<tr><td>Edoxaban 15, 30, 60mg tab</td><td>None</td><td>None</td><td>None</td><td>Apixaban
Rivaroxaban
Enoxaparin</td></tr>
<tr><td>Savaysa</td><td>None</td><td>None</td><td>None</td><td>Savella
Cervarix
Samsca</td></tr>
</table>
• High alert medication: The Institute for Safe Medication Practices (ISMP) includes edoxaban among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.
• Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, Facts and Comparisons, and ISMP Confused Drug Name List)
</td></tr>
</table>

Other Considerations

- **Pharmacokinetics/Pharmacodynamics:** Similar to other TSOACs, edoxaban exhibits peak pharmacodynamic effects within 1 to 2 hours. Edoxaban is eliminated primarily as unchanged drug in the urine. About 50% is eliminated renally, with the remainder eliminated by metabolism and biliary excretion. The elimination half-life is about 10 to 14 hours.[1]
- **Reversal:**

  - There is no specific reversal agent for edoxaban. Anticoagulant effects are expected to persist for about 24 hours after the last dose. There is no established routinely available test to monitor the anticoagulant effect of edoxaban.[1]
  - Management of bleeding should be individualized according to the specific situation but may reasonably include discontinuation of antithrombotic treatment and implementation of supportive measures (compression, surgical hemostasis, transfusion).
  - Hemodialysis is not expected to effectively clear edoxaban. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of edoxaban.[1]
  - Preliminary, phase 1 study in healthy subjects showed that 4-factor prothrombin complex concentrate exhibited dose dependent reversal of edoxaban as measured by bleeding duration, bleeding volume, and endogenous thrombin potential and partial reversal of prothrombin time.[10]
- **Adverse events upon discontinuation:**
  - An increased number of thromboembolic and bleeding events was observed when transitioning from a TSOAC to a vitamin K antagonist (e.g., warfarin) at the completion of the pivotal NVAF trials with rivaroxaban and apixaban.
  - A unique transitioning protocol for edoxaban was developed for the ENGAGE AF study intended to minimize periods of over- or under- anticoagulation and subsequent adverse events during the transition.[11] Patients switching from edoxaban to open label warfarin at the end of the study continued to receive half of their study dose of edoxaban and started warfarin concurrently. Frequent INR testing was performed, and an aggressive warfarin titration algorithm was used to help achieve therapeutic INRs rapidly. When a stable and therapeutic INR was reached, edoxaban was discontinued. Most patients had achieved at least one INR ≥2 by day 14.
  - About 70% of patients transitioned from study drug to open-label warfarin and 30% switched to another TSOAC; few stopped anticoagulation.
  - In the patients transitioning to warfarin, there were the same number of strokes (n=7) within 30 days in the high dose edoxaban and warfarin group.
- **Ongoing study:** Use of edoxaban in patients with NVAF undergoing electrical cardioversion is being evaluated in the multinational, prospective, randomized ENSURE-AF trial.

Dosing and Administration[1,2,4]

Assess CrCl before initiating therapy (CrCl was calculated using Cockcroft-Gault equation and actual body weight in clinical trials).

Administration:
- Edoxaban can be administered without regard to meals.
- No data are available evaluating the bioavailability of edoxaban if tablets are crushed or administered in liquids or in a feeding tube.

NVAF:
- The recommended dose of edoxaban is 60 mg orally once daily for patients with CrCl of 51 – 95 ml/min.
- *Reduced dose:* The FDA recommended dose of edoxaban is 30 mg orally once daily for patients with CrCl of 15* – 50 ml/min.
- *Limitation of use in NVAF:* Do not use edoxaban in patients with a CrCl >95 ml/min or <15* ml/min

VTE Treatment:
- The recommended dose of edoxaban is 60 mg orally once daily following 5 to 10 days of initial therapy with an injectable anticoagulant.
- *Reduced dose:* For patients with CrCl 15* to 50 ml/min, weight ≤60 kg, or who are taking certain concomitant P-gp inhibitor medications, the FDA recommended dose of edoxaban is 30 mg once daily based on clinical study data for the VTE treatment indication. (See Drug Drug Interactions sections for more details on P-gp inhibitor interactions)

***Note -** Clinical data are lacking in patients with CrCl 15-29 ml/min since these patients were excluded from clinical trials. PBM recommends avoiding use in patients with CrCl <30 ml/min in the absence of clinical data.

Discontinuation before surgery or procedures:

- It is recommended that edoxaban be discontinued at least 24 hours before invasive or surgical procedures due to risk of bleeding. If surgery cannot be delayed, the increased risk of bleeding while anticoagulated should be considered along with the urgency of the surgery or procedure.[1]
- Edoxaban can be restarted after the procedure or surgery once adequate hemostasis has been achieved, keeping in mind that the peak pharmacodynamic effect occurs within 1 to 2 hours after oral administration. If the patient cannot take oral medications after the intervention, use of a parenteral anticoagulant is recommended.[1]

Transitions to or from edoxaban and other anticoagulants:[1]

- When transitioning FROM warfarin TO edoxaban, discontinue warfarin and start edoxaban when INR is ≤2.5.
- When transitioning FROM oral non-vitamin K antagonist (e.g., TSOACs) TO edoxaban, discontinue the oral non-vitamin K antagonist and then start edoxaban at the time of the next scheduled dose of the non-vitamin K antagonist.
- When transitioning FROM LMWH TO edoxaban, discontinue LMWH and then start edoxaban at the time of the next scheduled dose of LMWH.
- When transitioning FROM edoxaban TO warfarin, reduce edoxaban dose by half (e.g., 60 mg to 30 mg) and start warfarin concomitantly. Check INR at least weekly just prior to the daily dose of edoxaban (to minimize interference of edoxaban on the INR test) and discontinue edoxaban when INR is stable and 2 or greater. Alternatively, edoxaban may be discontinued and an injectable anticoagulant administered along with warfarin, both starting at the time of the next scheduled dose of edoxaban. Discontinue edoxaban and parenteral anticoagulant when INR is stable and 2 or greater.
- When transitioning FROM edoxaban TO injectable anticoagulants, discontinue edoxaban and start the injectable anticoagulant at the time of the next scheduled edoxaban dose.

Special Populations (Adults)

	Comments
Elderly	• No significant age-related alterations in the pharmacokinetic parameters of edoxaban were found in studies.[1] • In ENGAGE AF, 40% of patients were 75 years of age or older. Primary efficacy and safety event rates were higher in older compared to younger patients, but the treatment effect of edoxaban vs. warfarin remained similar when evaluated by age.[2,3] • In HOKUSAI VTE, 14% of patients were 75 years of age or older. Subgroup analysis of the primary efficacy and safety endpoints revealed no significant interaction between treatment effect and age.[4,8]
Pregnancy	• Pregnancy Category C.[1] • There are no adequate and well controlled studies in pregnant women. Edoxaban should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1] • Women of childbearing potential were excluded from the ENGAGE AF trial.[12] In HOKUSAI VTE, women of childbearing potential were permitted in the trial if they were using contraception and were not pregnant or breastfeeding.[13] • There were 10 pregnancies reported in patients receiving edoxaban in the HOKUSAI VTE study, with drug exposure occurring in the first trimester. Outcomes included 6 live births, 3 elective abortions, and 1 spontaneous abortion in the first trimester.[1] • Safety and effectiveness have not been evaluated in labor and delivery.[1]

Lactation	• It is unknown whether edoxaban is present in human breast milk but was found in rat's milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants exposed to edoxaban, it is recommended to discontinue nursing or the drug.[1]
Renal Impairment	• About 50% of edoxaban is cleared renally. Based on pharmacokinetic study, edoxaban exposure increases with worsening renal impairment.[1] • Dose reductions are recommended in patients with CrCl of 50 ml/min and less. (See Dosing and Administration section)
Hepatic Impairment	• The pharmacokinetic and pharmacodynamic effects of edoxaban in patients with mild and moderate hepatic impairment (Child-Pugh A or B) were similar to effects in healthy controls.[1] • Edoxaban is not recommended in patients with moderate or severe (Child-Pugh B or C) hepatic impairment due to the intrinsic coagulation abnormalities that may be present in these patients.[1] • No dose reductions are recommended in patients with mild hepatic impairment.[1]
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

NVAF:

- As a class, TSOACs have been shown to be at least effective as warfarin for the reduction in the risk of all stroke and systemic embolism and carry a significantly lower risk of intracranial bleeding. With a few exceptions (i.e., increased GI bleeding with dabigatran, rivaroxaban, and edoxaban), TSOACs have an overall similar-to-favorable bleeding profile compared to warfarin. Given the lack of head-to-head study and differences in patient population and trial designs, it is unclear whether one TSOAC is superior to another. Compared to warfarin, TSOACs offer the convenience of less frequent laboratory monitoring. While the duration of action of TSOACs is significantly shorter than warfarin, the lack of specific reversal agent for the factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) is a significant concern for providers in the management of life threatening bleeding or urgent procedures. None of the TSOACs are recommended in patients with mechanical heart valves.
- The 2014 American Heart Association/American College of Cardiology Guidelines on the management of atrial fibrillation recommend oral anticoagulation in patients with NVAF and prior stroke, TIA, or a CHA_2DS_2VASc score of 2 or more.[14] Class I options for specific therapy are warfarin (Level of Evidence A) or TSOAC (dabigatran, rivaroxaban, or apixaban) (Level of Evidence B). The guidelines were published before the approval of edoxaban. Warfarin is recommended in patients with mechanical heart valves (Level of Evidence B), and TSOACs are recommended if unable to maintain a therapeutic INR (Level of Evidence C). For patients with a CHA_2DS_2VASc score of 1, no antithrombotic therapy, oral anticoagulant, or aspirin may be considered. The 2012 CHEST guidelines[15] and 2012 AHA/American Stroke Association Advisory on preventing stroke in atrial fibrillation[16] were also published prior to the availability of edoxaban. In general, the guidelines recognize TSOACs as alternatives to warfarin with a lower level of evidence supporting the recommendations for use.
- Edoxaban was noninferior to adjusted dose warfarin for the reduction of all cause stroke and systemic embolism in patients with NVAF; however, reduced efficacy was noted in the subgroup of patients with good renal function. Therefore, edoxaban should not be used in patients with a CrCl >95 ml/min. Edoxaban exhibited a favorable bleeding profile compared to warfarin except for an excess of GI bleeds.

VTE:

- Published prior to the availability of edoxaban, the 2012 ACCP CHEST Guidelines provide a weak preference (Grade 2C) for vitamin K antagonist over rivaroxaban or dabigatran in the acute and long term treatment of VTE (in patients with no cancer), stating that the evidence with each agent is of moderate quality because of imprecision for each outcome.[17]

- Edoxaban was noninferior to adjusted dose warfarin (following initial treatment with an injectable anticoagulant) in the reduction of recurrent, symptomatic VTE in patients presenting with acute VTE. Except for an excess of GI and vaginal bleeding, edoxaban was associated with a similar-to-lower risk of bleeding compared to warfarin.

General:

- Edoxaban is the fourth TSOAC approved in the U.S. Edoxaban has been shown to have an overall comparable efficacy and favorable safety profile to warfarin in both NVAF and VTE populations. Effects appear to be maintained in the elderly population, though only 14% of the VTE population were 75 years of age and older. Patients with good renal function (CrCl >95 ml/min) should not receive edoxaban for the treatment of NVAF. Reduced dosing for special situations was studied clinically and approved by FDA. Like rivaroxaban, edoxaban is dosed once daily. Dabigatran, rivaroxaban, and edoxaban have been associated with increased GI bleeding compared to warfarin in contemporary clinical trials; apixaban is the only TSOAC currently available in the U.S. not associated with an excess of events.
- Overall, there is moderate quality evidence on the use of edoxaban for the reduction of stroke and systemic embolism in patients with NVAF and for the reduction in the risk of recurrent, symptomatic VTE in patients with acute VTE (see Appendix A).

Prepared October 2015. Contact person: Lisa Longo, Pharm.D., BCPS, VA PBM Services

References

[1]SAVAYSA [package insert]. Daiichi Sankyo Co., LTD. Tokyo Japan. January 2015.
[2] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-2104.
[3] Supplement to: Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-2104.
[4] Hokusai Investigators, Buller HR, Grosso MA, Mercuri M, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369:1406-15.
[5] FDA Summary Review: Edoxaban. January 8, 2014. Accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206316Orig1Orig2s000SumR.pdf . (accessed on September 22, 2015).
[6] SAVAYSA Product Dossier. Daiichi Sankyo Co., LTD. Tokyo Japan. Version 1.1. March 10, 2015.
[7] SAVAYSA Drug Information Communication Letter. Daiichi Sankyo Co., Parsippany NJ. Information last reviewed August 27, 2015.
[8] Supplement to: Hokusai Investigators, Buller HR, Grosso MA, Mercuri M, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369:1406-15.
[9] FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee. October 30, 2014. Accessed at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm420704.pdf (accessed on September 10, 2015).
[10] Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation. 2015:131:82-90.
[11] Ruff CT, Giugliano RP, Braunwald E, et al. Transition of patients from blinded study drug to open-label anticoagulation. The ENGAGE AF-TIMI 48 Trial. J Am Coll Cardiol. 2014;64:576-84.
[12] Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the effective anticoagulation with factor Xa next generation in atrial fibrillation – thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010;160:635-641.e2.
[13] Raskob G, Buller H, Prins M, et al. Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study – methodological implications for clinical trials. J Thromb Haemost. 2013;11:1287-94.

[14] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.
[15] You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation. CHEST. 2012;141(2)(Suppl):e531S-75S.
[16] Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:3442-53.
[17] Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease. CHEST. 2012;141(2)(Suppl):e419S-e494S.

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.