Brand Name: Savaysa[1]

Generic Name: edoxaban[1]

Manufacturer: Daiichi Sankyo Co., LTD.[2]

Drug Class: factor Xa inhibitor[3]

Uses:

Labeled Uses:

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)[4]
- For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant[4]

Unlabeled Uses:

- Arthroplasty of knee, Total - Postoperative deep vein thrombosis; Prophylaxis[5]
- Arthroplasty of hip, Total - Postoperative venous thromboembolism; Prophylaxis[6]

Mechanism of Action:

Edoxaban is a selective inhibitor of factor Xa and does not require antithrombin III for antithrombotic activity. It inhibits free factor Xa and prothrombinase activity[3]. Inhibition of factor Xa decreases the generation of thrombin[3] and reduces thrombus formation[1]. Edoxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin[3]

Pharmacokinetics:

Absorption:

T_{max}	1-2 hours [1]
V_d	107 L [1]
$t_{½}$	10-14 hours [3]
Clearance	22 L/hr [1]
Protein binding	55% [1]
Bioavailability	62% [1]

Metabolism: Edoxaban is a P-glycoprotein substrate.[3] Unchanged Edoxaban is the predominant form in plasma. There is minimal metabolism via hydrolysis (mediated by carboxylesterase 1), conjugation, and oxidation by CYP3A4. The predominant metabolite M-4, formed by hydrolysis, is human-specific and active and reaches less than 10% of the exposure of the parent compound in healthy subjects. Exposure to the other metabolite is less than 5% of exposure to Edoxaban.[1]

Elimination: Edoxaban is eliminated primarily unchanged in the urine. Renal clearance (11 L/hour) accounts for approximately 50% of the total clearance of Edoxaban (22 L/hour). Metabolism and biliary/intestinal excretion account for the remaining clearance. The terminal elimination half-life of Edoxaban following oral administration is 10-14 hours [1]

Efficacy:

Fuji T, Fujita S, Kawai Y, Nakamura M, Kimura T, Fukuzawa M. Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V. Thromb J. 2015 Aug;13:27.

Study Design: Randomized, double-blind, double dummy, phase 3, multicenter, enoxaparin controlled, non-inferiority study with a parallel group design [6]

Description of Study: *Methods*: Six hundred ten patients 20-85 years of age undergoing unilateral total hip arthroplasty (THA) were randomized 1:1 to receive either oral edoxaban 30 mg once daily or subcutaneous enoxaparin 2,000 IU twice daily for 11-14 days. Treatment with edoxaban was administered within 6-24 hours after surgery and once daily each morning thereafter. Enoxaparin injection was administered 24-36 hours after surgery and twice daily from the following day onward. The primary efficacy endpoint was the incidence of VTE, including asymptomatic DVT and symptomatic PE or DVT. Secondary efficacy endpoints were the incidence of symptomatic DVT, proximal DVT, symptomatic PE or VTE-related death; the incidence of asymptomatic or symptomatic DVT; the incidence of symptomatic or proximal DVT; the incidence of symptomatic PE; the incidence of VTE-related deaths, and the incidence of all cause deaths. Safety endpoints included the incidences of major bleeding; CRNM bleeding; major or CRNM bleeding; any bleeding; and minor bleeding events from the start of treatment to the day after the end of treatment. Additional safety endpoints were the incidences of AEs and adverse drug reactions. The non-inferiority margin was set at 8% for the difference in the primary endpoint between the two groups, with a 1-sided significance level of 0.025. The number of patients necessary to verify non-inferiority was calculated to be 235 patients per treatment group. *Outcomes*: The incidence of VTE, based on venography and clinical surveillance, was 2.4% in the edoxaban group and 6.9% in the enoxaparin group ($P<0.001$). The absolute difference in the incidence of VTE was -4.5% (95% CI: -8.6,-0.9), which was within the non-inferiority margin set at 8%. Since the upper limit of the 95% CI of the absolute difference was <0%, the superiority of edoxaban over enoxaparin was demonstrated. There was no difference in the incidence of serious AE' between the edoxaban (3.0%) and enoxaparin (3.0%) treatment groups. The incidence of major or CRNM bleeding was 2.6% in the edoxaban group and 3.7% in the enoxaparin group ($P= 0.475$) [6]

Limitations: NSAID use was not properly distributed between groups since 98% of patients in the edoxaban group concomitantly used NSAID's compared to 81% in the enoxaparin group; this could have led to higher rates of minor bleeding in the edoxaban group. The dose of enoxaparin used (2,000 IU, twice daily) is a recommendation specific to Japan for VTE prevention and can't be extrapolated to other parts of the world. The study was funded by Daiichi Sankyo Co., Ltd, the manufacturer of edoxaban. In addition, Daiichi Sankyo Co., was involved in the study design and collection and analysis of data. All of the study authors were either consultants or employees of the company, introducing a potential conflict of interest. Each of these authors were involved in the interpretation of data and data analysis, introducing a potential conflict of interest and bias in results [6]

Conclusion: The study demonstrated the superiority of oral once-daily edoxaban 30 mg compared with twice-daily subcutaneous injection of enoxaparin 2000 IU for the prevention

of VTE in Japanese patients after THA, without an increased risk of bleeding or AEs. The favorable efficacy-to-safety balance of edoxaban suggests an attractive option for thromboprophylaxis in patients following THA. However, more studies need to be conducted in patients with different ethnic backgrounds since these results are primarily only relevant for the Japanese population [6]

Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406-15.

Study Design: Randomized, double-blind, double-dummy, non-inferiority, multinational clinical trial [7]

Description of the Study: *Methods*: 8,292 adult patients with acute, symptomatic DVT or PE (with or without DVT) all initially received open label heparin (enoxaparin or unfractionated heparin) for at least 5 days. The patients were then randomized to receive either edoxaban 60 mg orally or 30 mg orally, when warranted in selected patients, once daily or warfarin therapy. Treatment was carried out for 3-12 months; duration was determined by the treating physician on the basis of patient clinical features and patient preference. INR measurements were performed at least monthly. The primary efficacy outcome was recurrent symptomatic venous thromboembolism, defined as a composite of DVT or non-fatal or fatal PE. The principal safety outcome was major or clinically relevant non-major bleeding. Net clinical benefit was determined on the basis of the composite of symptomatic recurrent VTE or major bleeding. *Outcomes*: 4921 patients presented with DVT, and 3319 with a PE. In the patients receiving warfarin, time in the therapeutic range was 63.5%. Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (HR, 0.89; 95% CI, 0.70 to 1.13; $P < 0.001$ for non-inferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 (10.3%) in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; $P = 0.004$ for superiority). The rates of other adverse events were similar in the two groups. A total of 938 patients with PE had right ventricular dysfunction; the rate of recurrent VTE in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (HR, 0.52; 95% CI, 0.28 to 0.98). The most common adverse reactions were related to bleeding. Overall, bleeding events occurred in 21.7% of edoxaban patients compared with 25.6% of warfarin patients [7]

Limitations: Similar studies focused on a single drug approach which allowed them to guarantee that the effects seen were from edoxaban and not related to other study medications. Efficacy of edoxaban was not limited to only those patients who received the medication, thus efficacy could have been influenced by other therapies used in the study. Physicians were allowed to adjust the duration of treatment for the participants after 3 months according to their clinical judgment or according to evolving evidence but because this was a multicenter study, readers can't be assured that each physician acted in a similar manner when adjusting certain the duration of therapy for their patients. Conflicts of interest are present because four of the authors, Grosso, Mercuri, Middeldorp, and Schwocho, are affiliated with Daiichi Sankyo Pharma Development which makes edoxaban.

Conclusion: The study demonstrated comparable symptomatic events between edoxaban and warfarin. Edoxaban was non-inferior to warfarin for recurrent VTE in patients with acute symptomatic VTE who were treated for 3-12 months following heparin or enoxaparin therapy for at least 5 days. Treatment with edoxaban is associated with a significantly lower rate of clinically relevant non-major bleeding compared with warfarin. A major benefit of treatment with edoxaban compared to warfarin is edoxaban does not require routine blood testing [7]

Mega JL, Walker JR, Ruff CT, Vandell AG, Nordio F, Deenadayalu N, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomized, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015; 385: 2280–87.

Study Design: Randomized, double-blind, double-dummy, multi-center, multi-national, parallel-group design study [8]

Description of Study: *Methods***:** In the study 14,348 patients age 21 and older with nonvalvular atrial fibrillation (NVAF) within the previous 12 months, a $CHADS_2$ risk score $\geq$ 2, and anticoagulation planned for the duration of the trial, were enrolled in the genetic analysis results. Patients were randomly assigned in a 1:1:1 ratio to receive warfarin with a target INR of 2-3, or to a high dose (60 mg) or low dose (30mg) edoxaban once daily. A subgroup of patients was included in a pre-specified genetic analysis and genotyped for variants in CYP2C9 and VKORC1 to see whether patients with functional genetic variants were at higher risk of bleeding and would derive benefit from treatment with edoxaban. Outcomes were assessed from the start of study treatment to day 90 and then for an additional 90 days; patients could have events in both time periods. The primary outcome was to test whether genetic variants can identify patients who are at increased risk of bleeding with warfarin would derive a greater safety benefit with edoxaban. *Outcomes:* Of 4,833 patients taking warfarin, 2982 (61.7%) were classified as normal responders, 1711 (35.4%) as sensitive responders, and 140 (2.9%) as highly sensitive responders. Compared with normal responders, sensitive and highly sensitive responders spent greater proportions of time over-anticoagulated in the first 90 days of treatment (median 2.2%, IQR 0–20.2; 8.4%, 0–25.8; and 18.3%, 0–32.6; $P_{trend} < 0.0001$) and had increased risks of bleeding with warfarin (sensitive responders hazard ratio 1.31, 95% CI 1.05–1.64, P = 0.0179; highly sensitive responders 2.66, 1.69–4.19, P < 0.0001). Genotype added independent information beyond clinical risk scoring. During the first 90 days, treatment with edoxaban reduced bleeding more in sensitive and highly sensitive responders than in normal responders (higher-dose edoxaban $P_{interaction} = 0.0066$; lower-dose edoxaban $P_{interaction} = 0.0036$). After 90 days, the reduction in bleeding risk with edoxaban versus warfarin was similarly beneficial across genotypes [8]

Limitations: Early termination during the study resulted in a small number of participants to analyze and a small number of black patients in the pharmacogenetics cohort. Technical problems in regards to measurements during the study may have led to unreliable or uninterpretable data. Dose selection in this study was decided by the local investigator on the basis of the clinical profiles of patients. Due to the frequency of ischemic outcomes, the ability to confidently confirm or exclude pharmacogenetics interaction between warfarin patients that were normal responders compared to sensitive or highly sensitive responders was limited [8]

Conclusion: During the first 90 days of treatment with edoxaban reduced bleeding more in the sensitive and highly sensitive responders when compared to treatment with warfarin. After 90 days the reduction in bleeding risk with edoxaban versus warfarin was similarly beneficial across genotypes. The results of this study provide strong evidence that CYP2C9 and VKORC1 genotypes identify patients who are more likely to experience early bleeding with warfarin and who derive a greater early safety benefit from edoxaban compared with warfarin. For stroke prevention in such patients, a direct oral anticoagulant such as edoxaban offers a greater early safety benefit compared with warfarin. More studies are needed to further analyze more varied populations [8]

Contraindications:

Active pathological bleeding: Edoxaban is contraindicated in patients with active pathological bleeding. Edoxaban increases the risk of bleeding and can cause serious and potentially fatal bleeding. Patients should be monitored for signs and symptoms of bleeding. Evaluate signs or symptoms of blood loss promptly and discontinue Edoxaban in patients with active pathological bleeding [1]

Precautions:

Black Box Warning: Do not use in patients with CrCl greater than 95 mL/min due to reduced efficacy and increased risk of ischemic stroke. Assess CrCl with the Cockcroft-Gault equation prior to initiation of therapy [1,3,5]

Black Box Warning: Premature discontinuation may increase the risk of ischemic events. If discontinued for reasons other than pathological bleeding or therapy completion, consider covering with alternative anticoagulant [1,3,5]

Black Box Warning: Use caution in patients receiving neuraxial anesthesia or undergoing spinal puncture due to increased risk of spinal or epidural hematoma, which may cause permanent paralysis; monitoring recommended. Do not remove indwelling epidural catheters sooner than 12 hours after the last dose and wait 2 hours after catheter removal before administering edoxaban [1,3,5]

Cardiovascular: Use not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis [1,3,5]

Concomitant Use: Not recommended in patients with long-term use with other anticoagulants [1,3,5]

Concomitant Use: Avoid with P-glycoprotein inducers (ex. Rifampin) [1,3,5]

Hematologic: Serious and potentially fatal bleeding may occur; monitor for bleeding [1,3,5]

Hepatic: Not recommended in moderate-severe hepatic impairment (Child-Pugh B or C)[1,3,5]

Renal: Use not recommended for CrCl less than 15 mL/min. Dose adjustment necessary for renal impairment with CrCl 15 to 50 mL/min [1,3,5]

Monitoring Considerations: Patients should monitor for signs and symptoms of bleeding. Serum creatinine should be monitored and adjusted for as needed. Neurologic impairments should be monitored for as well [1]

Adverse Effects:

Treatment of NVAF

Hematologic
- Bleeding Events: Major (3.8%) [1,5]
- Anemia (9.6%) [1,5]

Hepatic
- Abnormal liver function tests (4.8%) [1,5]

Dermatologic
- Rash (4.2%) [1,3]

Neurologic
- Hemorrhagic cerebral infarction (0.3%) [1,5]
- Intracranial hemorrhage (0.5%) [1,5]

Treatment of DVT and PE

Hematologic
- Bleeding Events: Major (1.4%) [1,5]
- Bleeding Events: Clinically relevant, Non-major (7.2%) [1,5]
- Anemia (1.7%) [1,5]

Hepatic
- Abnormal liver function tests (7.8%) [1,5]

Dermatologic
- Rash (3.6%) [1,3]

Neurologic
- Intracranial hemorrhage (0.1%) [1,5]

Drug Interactions:

Major Drug Interactions

NSAIDS
- Concurrent use of edoxaban and NSAID's may result in increased risk of bleeding [5]

P-Glycoprotein (P-gp) Inducers (ex. Phenytoin, Carbamazepine, Rifampin, Phenobarbital)
- Concurrent use of edoxaban and selected P-gp inducers may result in decreased edoxaban efficacy [5]
- Avoid concomitant use of edoxaban with Rifampin[1]

Anticoagulants
- Concurrent use of edoxaban and anticoagulants may result in increased risk of bleeding [5]
- Short term co-administration of edoxaban and other anticoagulants may be needed for patients transitioning to or from edoxaban [1]

Antiplatelet Agents
- Concurrent use of edoxaban, an Anticoagulant, and antiplatelet agents may result in increased risk of bleeding [5]

Fibrinolytics (ex. Streptokinase, Urokinase, Alteplase, Recombinant Tenecteplase)

- Concurrent use of an Anticoagulant, such as edoxaban, and fibrinolytics may result in an increased risk of bleeding [5]

Abciximab

- Concurrent use of Abciximab and anticoagulants, such as edoxaban, may result in an increased risk of bleeding [5]

Moderate Drug Interactions

Ticagrelor

- Concurrent use of Ticagrelor and anticoagulants, such as edoxaban, may result in increased risk of bleeding [5]

Dosing/Administration:

Treatment of NVAF

- Assess CrCL using the Cockcroft-Gault equation before initiating therapy. Do not use edoxaban in patients with a CrCl > 95 mL/min [1]
- For patients with CrCl 50-95 mL/min the recommended dose is 60 mg once daily [1]
- For patients with CrCl 15-50 mL/min the recommended dose is 30 mg once daily [1]

Treatment of DVT and PE

- The recommended dose is 60 mg once daily following 5-10 days of initial therapy with a parenteral anticoagulant [1]
- For patients with CrCl 15-50 mL/min or who weight $\leq$ 60 kg or who are taking certain concomitant P-glycoprotein inhibitor medications the recommended dose is 30 mg once daily following 5-10 days of initial therapy with a parenteral anticoagulant [1]

Arthroplasty of knee, Total-Postoperative DVT; Prophylaxis (Off-Label Use)

- 30 mg once daily starting 6 to 24 hours after surgery and continuing for 11 to 14 days (study dose) [5]

Geriatric Use

- In clinical trials the efficacy and safety of edoxaban in elderly (65 years or older) and younger patients were similar [1]

Pediatric Use

- Safety and effectiveness in pediatric patients have not been established [1]

Renal Impairment

- CrCl 15-50 ml/min the recommended dose is 30 mg once daily [1]
- CrCl < 15ml/min edoxaban is not recommended [1]
- Hemodialysis does not significantly contribute to edoxaban clearance [1]

Hepatic Impairment

- Child-Pugh Class A: No dose adjustments [1]
- Child-Pugh Class B: Not recommended [1]
- Child-Pugh Class C: Not recommended [1]

Max Dosing Limits:

- Adults – 60 mg/day [3]
- Geriatric – 60 mg/day [3]
- Pediatrics – safety and efficacy have not been established [3]

Missed Dose:

- If a dose of edoxaban is missed, the dose should be taken as soon as possible on the same day. Dosing should resume the next day according to the normal dosing schedule. The dose should not be doubled to make up for a missed dose [1]

Transition to edoxaban:[1]

From	To	Recommendation
Warfarin or other Vitamin K Antagonist	*Edoxaban*	Discontinue warfarin and start edoxaban when the INR is ≤ 2.5
Oral anticoagulant other than warfarin or other Vitamin K Antagonists	*Edoxaban*	Discontinue current oral anticoagulant and start edoxaban at the time of the next scheduled dose of the other oral anticoagulant
Low Molecular Weight Heparin (LMWH)	*Edoxaban*	Discontinue LMWH and start edoxaban at the time of the next scheduled administration of LMWH
Unfractionated heparin	*Edoxaban*	Discontinue the infusion and start edoxaban 4 hours later

Transition to edoxaban:[1]

From	To	Recommendation
Edoxaban	Warfarin	Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and the warfarin continued
Edoxaban	Warfarin	Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved the parenteral anticoagulant should be discontinued and the warfarin continued
Edoxaban	Non Vitamin K dependent oral anticoagulants	Discontinue edoxaban and start the other oral anticoagulant at the time of the next dose of edoxaban
Edoxaban	Parenteral anticoagulants	Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban

Use in special circumstances:

Surgery and Other Interventions: Discontinue edoxaban at least 24 hours before invasive or surgical procedures due to risk of bleeding. If surgery can't be delayed, there is an increased risk of bleeding and risks should be weighed against the urgency of intervention. Edoxaban can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established; noting that the time to onset of pharmacodynamics effect is 1-2 hours. Administer a parenteral anticoagulant and then switch to oral edoxaban, if oral medication cannot be taken during or after surgical intervention [1]

Overdose: A specific reversal agent for edoxaban is not available.[3] Overdose of edoxaban increases the risk of bleeding. The following are not expected to reverse the anticoagulant effects of edoxaban: protamine sulfate, Vitamin K, and tranexamic acid. Hemodialysis does not significantly contribute to edoxaban clearance [1]

Pregnancy: Edoxaban is a pregnancy category C and adverse events were observed in animal studies.[4] There is 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]

Lactation: Edoxaban is not recommended to be used during lactation; it is unknown if it is excreted in human milk [4]

- Edoxaban was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from edoxaban, a decision should be made to discontinue nursing or discontinue edoxaban, taking into account the importance of the drug to the mother [1]

Labor and delivery: Safety and effectiveness of edoxaban during labor and delivery have not been studied in clinical studies. The risks of bleeding should be balanced with the risk of thrombotic events when considering the use of edoxaban in this setting [1]

Impaired Renal Function: The use of edoxaban is not recommended in patients with renal failure or severe renal impairment defined as CrCl less than 15 mL/min. Dose reductions are required in patients with CrCl 15 to 50 mL/min [3]

Moderate or Severe Hepatic Impairment: The use of edoxaban is not recommended in patients with moderate or severe hepatic impairment [5]

Conclusion:

Edoxaban is an effective anticoagulant when used as prophylaxis of stroke and systemic embolisms in patients with nonvalvular atrial fibrillation however; it should not be used in patients with a CrCl greater than 95 mL/min or less than 15 mL/min because of reduced efficacy in preventing ischemic strokes compared with warfarin treatment. Patients with a rapidly fluctuating CrCl should have their CrCl closely monitored and assessed using the Cockcroft-Gault equation to ensure their CrCl stays between 95-15 mL/min.[1] Edoxaban is non-inferior to warfarin in reducing the risk of stroke and systemic embolism however edoxaban is associated with significantly lower rates of major bleeding when compared with warfarin therapy.[6] Edoxaban is also an effective therapy for the treatment of deep vein thrombosis and pulmonary embolism when started 5 to 10 days after initial therapy with a parenteral anticoagulant. Edoxaban is non-inferior to warfarin for symptomatic recurrent venous thromboembolism and is associated with a significantly lower rate of clinically relevant non-major bleeding events compared with warfarin therapy.[7] Patients with CYP2C9 and VKORC1 genotypes are more likely to have greater early safety benefit from edoxaban compared to warfarin during the first 90 days of therapy.[8] While the higher dose of edoxaban doesn't show significant differences from other non-vitamin K dependent oral anticoagulants in terms of efficacy and safety, the 30 mg dose has some distinctive features. The better safety profile in terms of major bleedings compared to all other non-vitamin K dependent oral anticoagulants, and for gastrointestinal bleedings

compared to dabigatran and rivaroxaban, would make 30 mg edoxaban an option in patients with a high or very high risk of bleeding.[9] Patients can be converted to and from edoxaban and other anticoagulants including warfarin, non-vitamin K dependent oral agents and heparins. It should not be used in pediatric patients, adults with renal failure, including severe renal impairment, or adults with mild to moderate hepatic impairment.

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