Edoxaban (Savaysa): A Factor Xa Inhibitor

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INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia, is encountered in clinical practice with ever-increasing frequency. Older data suggest that the lifetime risk of AF in men and women older than 40 years of age is approximately one in four. The prevalence of AF has most likely increased due to the aging of the “baby-boomers” (AF is overwhelmingly a disease of age) and improved overall survival. While AF in itself is not fatal, it increases patients’ risk of stroke or thromboembolism by up to fivefold. Current treatment for AF is aimed at preventing its related complications—primarily stroke and thromboembolism. The primary prevention strategy for minimizing the risk of stroke in patients with AF is anticoagulation.

Venous thromboembolism (VTE) is one of the three major causes of death associated with cardiovascular disease. VTE encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE); left untreated, VTE may manifest as either one. The U.S. Surgeon General has declared PE the most common preventable cause of death among hospitalized patients.

For more than half a century, warfarin has remained the gold standard for anticoagulation. Since its approval for human medical use in 1954, warfarin continues to be the most widely prescribed oral anticoagulant in the U.S. for the treatment of AF, VTE, or both. A few years ago, new oral anticoagulants (NOACs) began entering the U.S. market and competing against warfarin, starting with Food and Drug Administration (FDA) approval on October 19, 2010, of dabigatran etexilate (Pradaxa, Boehringer Ingelheim) as the only direct thrombin inhibitor for the prevention of stroke in patients with nonvalvular AF.

Dabigatran provided a foundation for the approval of a new class of medications known as factor Xa (FXa) inhibitors. In the U.S., these medications include rivaroxaban (Xarelto, Janssen), apixaban (Eliquis, Bristol-Myers Squibb), and most recently edoxaban (Savaysa, Daiichi Sankyo). All of the FXa inhibitors have an FDA-approved indication for the prevention of stroke and systemic embolism in patients with nonvalvular AF (Table 1).

Edoxaban was approved in 2011 in Japan as Lixiana for the prevention of VTE in patients undergoing total knee-replacement surgery, total hip-replacement surgery, and hip-fracture surgery. Since then, two global phase 3 studies, ENGAGE AF-TIMI 48 and Hokusai-VTE, have studied separate indications for edoxaban’s use in the prevention of stroke or systemic embolic events in patients with nonvalvular AF. Edoxaban acts to selectively inhibit free factor Xa in the coagulation cascade, resulting in reduced thrombin generation and formation. Edoxaban delays clotting as shown by tests of prothrombin time (PT) and activated partial thromboplastin time (aPTT). However, the results of these tests do not reflect the efficacy of edoxaban and should not be used to guide clinical decisions regarding its anticoagulation effects.

PHARMACOLOGY

Chemical Composition

The empirical formula of edoxaban tosylate monohydrate is \( \text{C}_{24}\text{H}_{30}\text{ClN}_7\text{O}_4\text{S} \cdot \text{C}_7\text{H}_3\text{O}_2\text{S} \cdot \text{H}_2\text{O} \). The chemical structure is shown in Figure 1.

Pharmacodynamics

Edoxaban acts to selectively inhibit factor Xa in the coagulation cascade, resulting in reduced thrombin generation and formation. Edoxaban delays clotting as shown by tests of prothrombin time (PT) and activated partial thromboplastin time (aPTT). However, the results of these tests do not reflect the efficacy of edoxaban and should not be used to guide clinical decisions regarding its anticoagulation effects.

Pharmacokinetics

Absorption

Edoxaban is absorbed rapidly upon oral administration, providing peak plasma concentrations within one to two hours. The bioavailability of the tablet is 62%. Edoxaban can be taken without regard to meals, since food has not been shown to affect systemic exposure. No data are available regarding edoxaban’s bioavailability when crushed or mixed into foods or liquids or administered through a feeding tube.

Distribution

Edoxaban is biphasic with a steady-state volume of distribution (\( V_{\text{ss}} \)) of 107 L. Edoxaban does not exhibit high protein binding (approximately 55% in vitro). With its indicated once-daily dosing, edoxaban does not accumulate to a clinically significant level. Steady state is achieved within three days.
In plasma, edoxaban primarily exists in its parent form and is minimally metabolized by hydrolysis or conjugation/oxidation via CYP3A4. The predominant metabolite, M-4, is an active metabolite that is formed by hydrolysis and exists as less than 10% of the exposure of the parent compound.

Elimination

Edoxaban is primarily excreted unchanged in the urine. Renal clearance accounts for roughly half of the total clearance. The half-life of edoxaban is about 10 to 14 hours.

**CLINICAL EFFICACY**

**ENGAGE AF-TIMI 48**

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial was a three-group, randomized, double-blind, double-dummy, noninferiority trial comparing high-dose edoxaban (60 mg) and low-dose edoxaban (30 mg) with warfarin (titrated to an international normalized ratio [INR] of 2.0 to 3.0). The study took place at 1,393 centers in 46 countries.

Patients were included if they were at least 21 years of age, had a CHADS2 score of at least 2, had diagnosed AF within 12 months preceding randomization, and had planned anticoagulation therapy for the duration of the trial. Patients were excluded if they had AF due to a reversible disorder, an estimated creatinine clearance (CrCl) of 30 mL/min or less, a high risk of bleeding, use of dual antiplatelet therapy, moderate-to-severe mitral stenosis, acute coronary syndrome, coronary revascularization, a stroke within 30 days before randomization, or other indications for anticoagulation therapy.

A total of 21,105 patients were enrolled and underwent randomization (1:1:1) to receive the respective study drugs. Treatment took place for a median of 2.5 years and patients were followed for a median of 2.8 years. Throughout the study, if patients presented with the fol-
lowing three clinical factors—CrCl of 50 mL/min or less; low body weight (60 kg or less); or concomitant use of specific P-glycoprotein (P-gp) inhibitors, including verapamil, quinidine, or dronedarone—their edoxaban dose was decreased by 50%. This resulted in about 25% of patients across all treatment groups receiving a dose reduction at randomization, as well as an additional 7% (among those who initially received full doses) receiving dose reductions during the study. Decreases in creatinine clearance were the most common reason for dose reductions.

The primary efficacy endpoint was the occurrence of a first stroke (ischemic or hemorrhagic) or a systemic embolic event during the course of treatment or within three days of the last dose taken. This took place at a rate of 1.50% per year in the warfarin group compared with 1.18% per year (hazard ratio [HR], 0.79; P < 0.001) in the high-dose edoxaban group and 1.61% per year (HR, 1.07; P = 0.005) in the low-dose edoxaban group. The secondary outcome of mortality rate from a cardiovascular cause was lower in the high-dose edoxaban group (2.74%; HR, 0.86; P = 0.01) and the low-dose edoxaban group (2.71%; HR, 0.85; P = 0.008) compared to warfarin (3.17%).

The primary safety endpoint was the number of major bleeding events. Major bleeding occurred at a rate of 3.43% per year in the warfarin group, 2.75% per year (HR, 0.80; P < 0.001) in the high-dose edoxaban group, and 1.61% per year (HR, 0.47; P < 0.001) in the low-dose edoxaban group. Overall, bleeding was more frequent with use of warfarin than with either dose of edoxaban. However, gastrointestinal (GI) bleeding was more prevalent with the use of high-dose edoxaban than with the use of warfarin. The rate of GI bleeding was lowest with low-dose edoxaban.

Noninferiority to warfarin was established in this trial for both once-daily dosing regimens of edoxaban for the prevention of stroke or systemic embolism, and high-dose edoxaban was superior to warfarin. Edoxaban was also associated with significantly lower rates of bleeding and death from cardiovascular causes. The efficacy and safety of edoxaban have a dose-dependent relationship in the context of AF. **Hokusai-VTE Trial**

The Hokusai-VTE trial was a randomized, multicenter, double-blind clinical trial that was designed to evaluate the safety and efficacy of edoxaban compared with warfarin for the treatment of VTE. The study compared heparin (enoxaparin or unfractionated heparin) followed by edoxaban versus heparin followed by warfarin in patients for the treatment of DVT, PE, or both. Patients received active treatment for three to 12 months and were followed for 12 months afterward regardless of the duration of therapy.

Patients were included if they were at least 18 years of age and had objectively diagnosed, acute, symptomatic DVT or acute, symptomatic PE (or both). The study encouraged the enrollment of all patients, including those with extensive disease—much like what is encountered in real-world practice. Among those excluded were patients who had contraindications to heparin or warfarin, who had another indication for warfarin therapy, who had cancer for which long-term treatment with low-molecular-weight heparin was anticipated, who were receiving aspirin therapy of more than 100 mg daily, who were on dual antiplatelet therapy, or who had a CrCl of less than 30 mL/min.

A total of 8,292 patients were enrolled and underwent randomization (1:1) at 439 centers in 37 countries. As with AF, the starting dose was a 60-mg tablet by mouth once daily, which was adjusted to a 30-mg dose for the same renal-function reasons. Of the 5,049 patients who initially received full-dose edoxaban, 3,205 patients (63.6%) were treated in the high-dose edoxaban group and 1,844 patients (36.4%) in the low-dose edoxaban group. The secondary outcome of mortality was decreased by 50%. This resulted in 8.5%; HR, 0.81; P = 0.004 for superiority) in the edoxaban group and 423 of 4,122 patients (approximately 10.3%) in the warfarin group. Major bleeding—defined as overt bleeding that was associated with a decrease in hemoglobin of 2 g/dL or more, required a transfusion of two or more units of blood, occurred at a critical site, or contributed to death—occurred in 56 patients (1.4%) in the edoxaban group and 66 patients (1.6%) in the warfarin group. Of the patients who qualified for low-dose edoxaban, clinically relevant bleeding occurred in 58 of the 733 patients (7.9%) in the edoxaban group and in 92 of the 719 patients (12.8%) in the warfarin group (HR, 0.62). Overall, the incidence of death and other adverse effects was similar across both groups.

Edoxaban once daily was noninferior to standard therapy with warfarin for the treatment of VTE after initial therapy with heparin. While high-dose edoxaban resulted in less fatal and intracranial bleeding, the between-group difference with respect to major bleeding did not reach statistical significance. Having the dose adjusted to 30 mg maintained efficacy with significantly less bleeding than that observed in the warfarin group.

**SAFETY AND TOLERABILITY**

**Boxed Warnings8–10**

Edoxaban has three boxed warnings, two of which are shared by the rest of its pharmacological class. One boxed warning is unique to edoxaban—reduced efficacy in nonvalvular AF patients with a CrCl of less than 95 mL/min (calculated by the Cockcroft–Gault equation). This is most likely due to the strong relationship between the blood levels of edoxaban and corresponding renal function.

The other two boxed warnings are identical among the factor Xa inhibitors: premature discontinuation of edoxaban increases the risk of ischemic events, and spinal/epidural hematomas may occur in patients who are subsequently

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undergoing spinal puncture or receiving neuraxial anesthesia while receiving edoxaban.

Warnings and Precautions

Edoxaban is contraindicated in patients with active pathological bleeding. As previously mentioned, edoxaban should not be initiated in patients with an estimated CrCl of less than 95 mL/min due to high-dose edoxaban’s association with an increased rate of ischemic stroke compared to patients treated with warfarin. As with any anticoagulant, by its very nature edoxaban increases the risk of bleeding to a degree that could potentially be fatal. Similar to the other medications of its class, there is currently no direct reversal agent for edoxaban and its effects may persist for up to 24 hours after the last dose.

For patients who undergo neuraxial anesthesia or a spinal/epidural puncture, the risk of developing an epidural or spinal hematoma is increased with the use of antithrombotic agents. Indwelling epidural or intrathecal catheters should not be removed less than 12 hours after the last dose of edoxaban is administered. Likewise, the next dose of edoxaban should not be administered less than two hours after the removal of the catheter. Clinical judgment should be used in these scenarios to consider the risk versus benefit in patients who have received or are about to receive anticoagulation.

The use of edoxaban is not recommended in patients who have mechanical heart valves or who suffer from moderate-to-severe mitral stenosis. There are no data for the use of edoxaban in these patient populations.

Drug Interactions

Studies suggest that edoxaban does not inhibit any major cytochrome P450 enzymes (including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) and does not induce CYP1A2, CYP3A4, or P-gp transporter (MDR1). Despite being a substrate of P-gp transporter, current data suggest that edoxaban does not inhibit P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3. *In vitro* data also suggest that edoxaban concentrations are increased when it is coadministered with P-gp inhibitors, including ketoconazole, quinidine, verapamil, erythromycin, cyclosporine, amiodarone, and dronedarone. When edoxaban is coadministered with a P-gp inducer such as rifampin, the area under the curve (AUC) of edoxaban is decreased.

When coadministered with digoxin, edoxaban increased the peak concentration (Cmax) of digoxin with no change in AUC. Edoxaban had no effect on the Cmax and AUC of quinidine when they were coadministered. When coadministered with verapamil, edoxaban decreased the Cmax and AUC of verapamil by 14% and 16%, respectively.

**Dosage and Administration**

Edoxaban is FDA-approved for two indications: reduction in the risk of stroke and systemic embolism in NVAF, and the treatment of DVT and PE.

For reducing the risk of stroke and systemic embolism in nonvalvular AF, the recommended dose of edoxaban is one 60-mg tablet taken by mouth once daily. As previously mentioned, edoxaban should not be initiated in patients who have a CrCl of less than 95 mL/min as calculated by the Cockcroft–Gault equation. Reducing the dose by half (to 30 mg once daily) is recommended for patients whose CrCl is 15 to 50 mL/min. Edoxaban is not readily removed by hemodialysis (less than 7% reduced total edoxaban exposure in four hours).

For the treatment of DVT and PE, the recommended dose of edoxaban is 60 mg taken by mouth once daily following five to 10 days of initial therapy with a parenteral anticoagulant (low-molecular-weight heparin [LMWH] or unfractionated heparin). The dose of edoxaban adjusted for renal problems in this indication is the same as it is in patients with nonvalvular AF: For patients whose CrCl is 15 to 50 mL/min, the recommended dose is 30 mg once daily. The 30-mg once-daily dose is also recommended in patients who weigh 60 kg or less (about 132 pounds) and patients who are concomitantly taking P-gp inhibitors (verapamil, quinidine, or dronedarone).

There are no viable data for the use of edoxaban in pregnant women. Clinical judgment should be used in considering the administration of edoxaban in pregnant women. Clinical judgment should be used in considering the administration of edoxaban in pregnant patients, factoring in the potential benefit versus the potential risk to the fetus. Doses anywhere from three to 49 times the human dose have been tested in pregnant rats and rabbits, with embryofetal toxicities occurring at maternally toxic doses.

Specific dosing instructions cover the transition to and from edoxaban to warfarin, NOACs, LMWH, or unfractionated heparin. The recommendations for transitioning to edoxaban from warfarin differ slightly from the rest of its pharmacological class. Specific instructions for transitioning from edoxaban to warfarin are backed by clinical data, which are not available for the other NOACS. See Table 2 and ‘Table 3 for the manufacturers’ full recommendations.

**P&T Committee Considerations**

Edoxaban is available as 15-, 30-, and 60-mg tablets. For its two approved indications, the standard dose is 60 mg per day for most patients. This is adjusted to 30 mg per day for patients who fall under the manufacturer’s recommendations that take into account weight, creatinine clearance, concomitant therapy with specific P-gp inhibitors, and other factors. The 15-mg dose is reserved for patients who are being converted to warfarin and take 30 mg per day.

The most commonly used strength will be the 60-mg tablet; 50 of these tablets cost $554.40, or about $11.09/tablet. It is important to note that apixaban is generally dosed twice daily, making it slightly more expensive than other factor Xa inhibitors, with a maintenance dose costing about $12.60 per day. See Table 4 for comparative pricing.

**Conclusion**

Edoxaban provides hospitals and formularies with an alternative to the other NOACs. It is associated with less frequent bleeding (except gastrointestinal) than warfarin, has minimal risk of drug interactions, and has the advantage of once-daily dosing. Edoxaban’s efficacy has been well established since July 2011 in Japan. As with all NOACs, its long-term safety remains a question.

**References**


### Table 2 Recommendations for Transition From Other Anticoagulants to Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>From Warfarin to:</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Discontinue warfarin and start edoxaban when international normalized ratio (INR) is ≤ 2.5.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Discontinue warfarin and start rivaroxaban when INR is ≤ 3.0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Discontinue warfarin and start apixaban when INR is ≤ 2.0.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From Oral Anticoagulant Other Than Warfarin to:**

| Edoxaban                          | Discontinue current oral anticoagulant and start edoxaban at the time of the next scheduled dose of the other oral anticoagulant. |
| Rivaroxaban                       | Start rivaroxaban 0 to 2 hours prior to next scheduled evening administration of the other oral anticoagulant. |
| Apixaban                          | Discontinue current anticoagulant and begin apixaban at the time of the next scheduled dose. |

**From Low-Molecular-Weight Heparin (LMWH) to:**

| Edoxaban                          | Discontinue LMWH and start edoxaban at the time of the next scheduled administration of LMWH. |
| Rivaroxaban                       | Start rivaroxaban 0 to 2 hours prior to next scheduled evening administration of LMWH. |
| Apixaban                          | Discontinue LMWH and begin apixaban at the time of the next scheduled LMWH dose. |

**From Unfractionated Heparin to:**

| Edoxaban                          | Discontinue the infusion and start edoxaban 4 hours later. |
| Rivaroxaban                       | Discontinue the infusion and start rivaroxaban at the same time. |
| Apixaban                          | Discontinue current anticoagulant and begin apixaban at the time of the next scheduled dose. |

### Table 3 Recommendations for Transition From Factor Xa Inhibitors to Other Anticoagulants

**To Warfarin From:**

| Edoxaban                          | • For patients on edoxaban 60 mg, reduce dose to 30 mg and begin warfarin concomitantly. |
|                                   | • For patients on edoxaban 30 mg, reduce dose to 15 mg and begin warfarin concomitantly. International normalized ratio (INR) must be measured at least weekly, just prior to daily dose of edoxaban. Once stable INR ≥ 2.0 is achieved, discontinue edoxaban and continue warfarin. |
| Rivaroxaban                       | No clinical trials support a recommendation for converting patients from rivaroxaban to warfarin. One approach: discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time of the next scheduled dose of rivaroxaban. |
| Apixaban                          | If continued anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time of the next scheduled dose of apixaban; discontinue the parenteral anticoagulant once INR reaches acceptable range. |

**To Oral Anticoagulant Other Than Warfarin From:**

| Edoxaban                          | Discontinue edoxaban and start the other oral anticoagulant at the time of the next scheduled dose of edoxaban. |
| Rivaroxaban                       | Discontinue rivaroxaban and give first dose of the other anticoagulant at the time of the next scheduled dose of rivaroxaban. |
| Apixaban                          | Discontinue apixaban and begin the other oral anticoagulant at the time of the next scheduled dose of apixaban. |

**To Parenteral Anticoagulant From:**

| Edoxaban                          | Discontinue edoxaban and start parenteral anticoagulant at the time of the next scheduled dose of edoxaban. |
| Rivaroxaban                       | Discontinue rivaroxaban and give first dose of the other anticoagulant at the time of the next scheduled dose of rivaroxaban. |
| Apixaban                          | Discontinue apixaban and begin parenteral anticoagulant at the time of the next scheduled dose of apixaban. |

### Table 4 Factor Xa Inhibitor Strengths and Pricing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strengths</th>
<th>30-Day Supply*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>15-mg, 30-mg, and 60-mg tablets</td>
<td>~ $333 for all strengths</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10-mg, 15-mg, and 20-mg tablets</td>
<td>~ $378 for all strengths</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5-mg and 5-mg tablets</td>
<td>~ $378 for all strengths</td>
</tr>
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* Average wholesale price for recommended dose, rounded to the nearest dollar.

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