Edoxaban: an Investigational Factor Xa Inhibitor

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an increased prevalence in older adults. The estimated lifetime risk of developing AF is one in four for both men and women older than 40 years of age. AF is also an independent risk factor for stroke. This increased risk for stroke is present in younger patients and increases significantly with advancing age. The primary modality for reducing the risk of stroke in patients with AF is chronic anticoagulation.

Venous thromboembolism (VTE) is another serious condition in which an imbalance exists between clotting factors and endogenous anticoagulants, resulting in thrombosis. There are many risk factors for the development of VTE; blood clots can affect a wide variety of patients from ambulatory to institutional settings. Prevention and treatment options include both parenteral and oral medications.

Over the past few years, a number of new oral anticoagulants have been approved for the treatment of patients with AF, VTE, or both. Prior to the approval of dabigatran, rivaroxaban, and apixaban, warfarin was the only oral anticoagulant available in the United States. In October 2010, dabigatran was approved by the Food and Drug Administration (FDA) and became the only oral direct thrombin inhibitor available for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF; more recently, dabigatran was approved for the treatment of and reduction in the risk of recurrent VTE.

In November 2011 and December 2012, the FDA approved rivaroxaban and apixaban, respectively. These oral factor Xa inhibitors are indicated for the prevention of stroke and systemic embolism associated with nonvalvular AF, for the prevention of VTE in patients following knee or hip replacement surgery, and for the treatment of VTE and the reduction in the risk of recurrent VTE.

In January 2014, the Daiichi Sankyo Company submitted a new drug application (NDA) for another oral direct factor Xa inhibitor, edoxaban (Savaysa). Approval has been requested for the following indications: reduction in the risk of stroke and systemic embolic events in patients with nonvalvular AF; treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE); and prevention of recurrent symptomatic VTE. Promising results from large clinical studies suggest that this new anticoagulant will likely be a competitor to the other oral treatment options mentioned above.

Table 1 provides an overview of the oral anticoagulants.

PHARMACOLOGY AND MECHANISM OF ACTION

Edoxaban is a highly specific, direct inhibitor of factor Xa. Under normal circumstances, coagulation factors are successively activated along both intrinsic and extrinsic pathways that converge with the activation of factor Xa. Thrombin and fibrin are subsequently generated, leading to the production of a fibrin clot.

PHARMACOKINETICS AND PHARMACODYNAMICS

Edoxaban is absorbed rapidly, and food has no significant effect on its pharmacokinetics or pharmacodynamics. Once absorbed, edoxaban is present mostly in the parent drug form; however, there are several metabolites. Those with the highest concentration are produced via hydrolysis, and some minor metabolites are formed through cytochrome P450 3A enzymes. Bioavailability is comparable between tablet and solution formulations, although peak plasma concentration (Cmax) and other pharmacodynamic markers vary among the formulations. Peak concentrations are achieved one to two hours after the administration of a dose. Edoxaban distributes to extravascular tissues with relatively low protein binding (40% to 59%), remaining consistent at two, six, and 12 hours after the dosing interval. The half-life ranges from 5.8 to 10.7 hours with both the tablet and solution formulations (in single- and multiple-dose regimens). Elimination occurs via the kidneys at a rate higher than glomerular filtration, suggesting active secretion into the kidney. Approximately 60% of edoxaban can be detected in the feces and 40% in the urine.

CLINICAL Efficacy

The NDA submission for edoxaban is based on data from an extensive global clinical trial program that compared treatment with once-daily edoxaban to warfarin, a current standard of care for patients with AF or VTE. The two clinical trials that formed the basis of the submission, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial and the Hokusai-VTE trial, are the largest comparative trials of a novel oral anticoagulant in these patient populations, involving 21,105 and 8,292 patients, respectively.

ENGAGE AF-TIMI 48

In this double-blind, double-dummy trial, 21,105 patients (median age, 72 years) with moderate-risk to high-risk AF were randomized (1:1:1) to receive either warfarin once daily (dosed to an international normalized ratio [INR] goal of 2 to 3), high-dose edoxaban once daily (60 mg), or low-dose edoxaban once daily (30 mg). The study was conducted at 1,393 centers in 46 countries. Patients were evaluated using CHADS2 (an AF
stroke risk assessment that takes into account heart failure, hypertension, advanced age, diabetes, and prior stroke or transient ischemic attack). Participants were excluded if they had: reversible AF, an estimated creatinine clearance of less than 30 mL/min, high risk of bleeding, dual antiplatelet therapy, moderate-to-severe mitral stenosis, acute coronary syndromes, coronary revascularization, stroke within 30 days of randomization, or other indications for anticoagulant treatment. Throughout the study, doses of edoxaban were decreased by 50% in those groups if creatinine clearance was estimated to be 30 to 50 mL/minute, body weight was less than 60 kg, or there was concomitant use of verapamil, quinidine, dronedarone, or other P-glycoprotein inhibitors.

The aim of this trial was to compare the two edoxaban regimens to warfarin in patients with AF and a moderate-to-high risk of stroke (median follow-up, 2.8 years). The primary efficacy endpoint was time to first stroke or systemic embolism. Each edoxaban regimen was initially tested for noninferiority to warfarin; however, if either edoxaban arm met the prespecified criteria for noninferiority, a secondary analysis for superiority to warfarin was performed with the intention-to-treat data.

Premature and complete discontinuation of treatment occurred in 2,417 patients who had received warfarin, 2,415 patients who had received high-dose edoxaban, and 2,309 patients who had received low-dose edoxaban. In the warfarin arm, patients were found to have an INR range between 1.8 and 3.2 for 83.1% of the treatment period, and a mean time of 64.9 ± 18.7% within the therapeutic range during the treatment period.

During the treatment period, a stroke or systemic embolic event occurred among 232 patients in the warfarin arm (1.50% per year), 182 patients in the high-dose edoxaban arm (1.18% per year; hazard ratio [HR] versus warfarin, 0.79; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority), and 253 patients in the low-dose edoxaban arm (1.61% per year; HR versus warfarin, 1.13; 0.87; $P = 0.08$), and 2.04% in the low-dose edoxaban arm (HR versus warfarin, 1.13, $P = 0.10$).

Prespecified secondary outcomes included the annualized rate of death from cardiovascular causes and the annualized rate of death from any cause, stroke, systemic embolic event, or major bleeding. High-dose and low-dose edoxaban treatment arms were associated with lower annualized rates of death from cardiovascular causes than warfarin (2.74% [HR versus warfarin, 0.86; $P = 0.01$], 2.71% [HR versus warfarin, 0.85; $P = 0.008$],

### Table 1 Overview of Oral Anticoagulant Agents in the U.S.

<table>
<thead>
<tr>
<th>Drug (Brand Name, Manufacturer)</th>
<th>Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals)</th>
<th>Rivaroxaban (Xarelto, Janssen Pharmaceuticals)</th>
<th>Apixaban (Eliquis, Bristol-Myers Squibb/Pfizer)</th>
<th>Edoxaban (Savaysa, Daiichi-Sankyo)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
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<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>3–7%</td>
<td>66–100% (dose dependent)</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>92–95%</td>
<td>87%</td>
<td>40–59%</td>
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<tr>
<td>Coagulation monitoring required</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>12–17</td>
<td>5–9</td>
<td>12</td>
<td>5.8–10.7</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal and hepatic</td>
<td>Renal and fecal</td>
<td>Renal and hepatic</td>
</tr>
<tr>
<td>Renal dose adjustment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (based on clinical trials)</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Substrate of P-gp</td>
<td>Substrate of CYP450 3A4/5, 2J2, and P-gp</td>
<td>Substrate of CYP450 3A4 and P-gp</td>
<td>Substrate of P-gp</td>
</tr>
<tr>
<td>Reversal agent approved</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>Not expected</td>
<td>Not expected</td>
<td>Data not available</td>
</tr>
<tr>
<td>Indications</td>
<td>Reduce stroke and systemic embolism in nonvalvular AF; treatment and reduction in the risk of recurrent VTE</td>
<td>Reduce stroke and systemic embolism in nonvalvular AF; treatment of DVT or PE or prevention of their recurrence; prophylaxis of DVT in those undergoing hip or knee surgery</td>
<td>Reduce stroke and systemic embolism in nonvalvular AF; prophylaxis of DVT in those undergoing hip or knee surgery; treatment of DVT and PE; reduction in the risk of recurrent DVT and PE</td>
<td>Reduce stroke and systemic embolism in nonvalvular AF; treatment of DVT or PE; prevention of recurrent, symptomatic VTE</td>
</tr>
</tbody>
</table>

* FDA approval pending

AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism; P-gp = P-glycoprotein; VTE = venous thromboembolism
and 3.17%, respectively), as well as death from any cause, stroke, systemic embolic event, or major bleeding (7.26% [HR versus warfarin, 0.89; \( P = 0.003 \)], 6.79% [HR versus warfarin, 0.83; \( P = 0.001 \)], and 8.11%, respectively).

The authors concluded that both edoxaban doses were noninferior to well-managed warfarin for the prevention of stroke and systemic embolism, and that high-dose edoxaban was also superior to warfarin. In addition, edoxaban was associated with significantly lower rates of cardiovascular events, death, stroke, systemic embolic event, or major bleeding.

**Hokusai-VTE**

This double-blind, multicenter, multinational trial aimed to evaluate the efficacy and safety of edoxaban compared with warfarin in the treatment of VTE. Eight thousand ninety-two patients with VTE were randomized to receive either edoxaban 60 mg once daily (adjusted to 30 mg once daily in participants whose creatinine clearance was 30 to 50 mL/min, whose body weight was less than 60 kg, or who were taking potent P-glycoprotein inhibitors) or warfarin (dosed to an INR goal of 2 to 3), after at least five days with open-label enoxaparin or unfractionated heparin. The primary efficacy outcome was the recurrence of symptomatic VTE. Patients received active treatment for three to 12 months, but were followed for 12 months despite duration of therapy. Exclusion criteria included, but were not limited to, contraindications for heparin or warfarin, additional indication(s) for warfarin treatment, aspirin therapy at a dose of more than 100 mg daily, dual antiplatelet therapy, or creatinine clearance of less than 30 mL/min.

One hundred eighty-one patients in the edoxaban arm failed to complete the overall study period compared with 167 patients assigned to warfarin. Adherence to edoxaban was 80% in more than 90% of the patients in that arm. Patients in the warfarin arm were reported to have been within therapeutic range (INR between 2 and 3) for 63.3% of the study period.

During the overall study period, 130 patients (3.2%) in the edoxaban arm and 146 patients (3.5%) in the warfarin arm experienced a recurrence of VTE (HR with edoxaban, 0.89; \( P < 0.001 \) for non-inferiority). No statistically significant difference was reported in the recurrence of VTE between participants in the edoxaban arm who received the adjusted 30-mg once-daily dose and participants in the warfarin arm. The authors concluded that edoxaban once daily was noninferior to standard therapy with well-managed warfarin for the treatment of VTE after initial therapy with enoxaparin or unfractionated heparin.

**ADVERSE EFFECTS**

The primary safety endpoints for the ENGAGE AF-TIMI 48 and Hokusai-VTE trials were major bleeding or clinically relevant nonmajor bleeding. Compared with warfarin, edoxaban was generally associated with lower dose-related bleeding. In ENGAGE AF-TIMI 48, the annualized rate of major bleeding was 3.43% with warfarin versus 2.75% (HR, 0.80; \( P < 0.001 \)) with high-dose edoxaban and 1.61% with low-dose edoxaban (HR, 0.47; \( P < 0.001 \)). The annualized rate of major gastrointestinal bleeding was 1.23%, 1.51% (HR, 1.23; \( P < 0.003 \)), and 0.82% (HR, 0.67; \( P < 0.001 \)), respectively. The rates of other adverse events were similar among all treatment arms. In the Hokusai-VTE study, 10.3% of participants in the warfarin arm and 8.5% of those in the edoxaban arm (HR, 0.81; \( P = 0.004 \)) had a major or clinically relevant nonmajor bleed. The rates of other adverse events were similar in both arms.

**DRUG INTERACTIONS**

Edoxaban is a substrate of the efflux transporter P-glycoprotein. Coadministration with strong P-glycoproteins (i.e., verapamil, quinidine, or dronedarone) has been shown to increase total exposure of edoxaban by 50%. Coadministration with other P-glycoprotein substrates (i.e., atorvastatin or digoxin) has only minor effects on the pharmacokinetics of edoxaban.

**MACRINDICATIONS, PRECAUTIONS AND WARNINGS**

Contraindications, precautions, and warning for edoxaban use have not yet been determined. However, should edoxaban gain FDA approval, these may be similar to those of other oral factor Xa inhibitors (e.g., a history of hypersensitivity reactions and active bleeding).

**INDICATIONS AND USAGE**

Edoxaban is approved in Japan for the prevention of VTE following major orthopedic surgery. In the U.S., Daiichi Sankyo is awaiting a response from the FDA regarding its NDA for oral, once-daily administration of edoxaban for the reduction of stroke risk and systemic embolic events in patients with nonvalvular AF, the treatment of DVT or PE, and the prevention of recurrent, symptomatic VTE.

**DOSE AND ADMINISTRATION**

Doses of edoxaban studied in the clinical trials cited above included 60 mg orally once daily and 30 mg orally once daily for persons with an increased risk of bleeding (e.g., renal insufficiency and low body weight).

**CONCLUSION**

Edoxaban is another oral factor Xa inhibitor currently under review for approval in the treatment of AF and VTE. Having demonstrated lower rates of major bleeding, minimal risk of drug interactions, and convenient once-daily dosing, it has the potential to become a serious competitor to the currently available agents.

**REFERENCES**


