Edoxaban (Savaysa) – The Fourth New Oral Anticoagulant

The FDA has approved edoxaban (Savaysa – Daiichi Sankyo), a once-daily, oral, direct factor Xa inhibitor, for treatment of venous thromboembolism (VTE) and for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It is the fourth new oral anticoagulant to be approved for VTE and nonvalvular atrial fibrillation.

**STANDARD TREATMENT – Acute VTE** (deep vein thrombosis or pulmonary embolism) is usually treated initially with a parenteral anticoagulant such as unfractionated heparin, low molecular weight heparin (LMWH), or fondaparinux (Arixtra, and generics). Warfarin (Coumadin, and others) is started on the same day as parenteral therapy and titrated to an INR of 2-3. After ≥5 days, the parenteral anticoagulant is stopped and warfarin is continued as monotherapy. The new oral anticoagulants dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) all appear to be effective and safe alternatives to warfarin for treatment of acute VTE, but data in elderly patients and those with significant comorbidities are limited. Treatment of acute VTE usually continues for at least 3 months.1,2

In patients with nonvalvular atrial fibrillation, dabigatran, rivaroxaban, and apixaban all appear to be at least as effective as warfarin in preventing stroke, with significantly lower rates of intracranial bleeding and hemorrhagic stroke.3-5 Patients with atrial fibrillation associated with a mechanical valve or moderate to severe mitral stenosis should take warfarin.

**WARFARIN vs. NEW ORAL ANTICOAGULANTS** – Use of warfarin is complicated by the need for frequent monitoring of the INR, dietary restrictions, and concerns about its interactions with many other drugs. The new oral anticoagulants do not require routine INR-type monitoring, have no dietary restrictions, and may have fewer drug interactions than warfarin, but there is no fixed method for determining the extent of their anticoagulant effect, they have short half-lives that increase the risk of thrombosis with missed doses, and they are not recommended for use in patients with end-stage renal disease. No established antidote is currently available for these new drugs, but their anticoagulant effect may be reversed by prothrombin complex concentrate, and clinical studies of more specific reversal agents are in progress.5-7

**PHARMACOKINETICS** – Because of its high renal clearance, blood levels of edoxaban are higher in patients with decreased renal function. A pharmacokinetic study summarized in the package insert found that systemic exposure to edoxaban was >70% higher among patients with a CrCl ≤50 mL/min than among those with a CrCl ≥80 mL/min.

**CLINICAL STUDIES** – Edoxaban 60 mg/day (or 30 mg/day in patients with CrCl 30-50 mL/min, weight ≤60 kg, or concomitant use of P-glycoprotein inhibitors) has been compared to warfarin (INR 2-3) for both VTE and nonvalvular atrial fibrillation.3-5

**Venous Thromboembolism** – In a randomized, double-blind, 12-month noninferiority trial (Hokusai-VTE) in 8240 patients with acute VTE first treated with unfractionated heparin or LMWH, edoxaban was noninferior to warfarin in preventing symptomatic recurrent VTE (the primary endpoint), which occurred in 3.2% of patients taking edoxaban and 3.5% of those on warfarin. Patients taking edoxaban had a significantly lower rate of major or clinically relevant non-major bleeding (8.5% vs. 10.3%). There were
Table 2. Oral Anticoagulants for VTE and Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Usual Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin – generic</td>
<td>Vitamin K antagonist</td>
<td>2-10 mg² once/d</td>
<td>$7.90</td>
</tr>
<tr>
<td>Coumadin (BMS)</td>
<td></td>
<td></td>
<td>53.70</td>
</tr>
<tr>
<td>Dabigatran etexilate – Pradaxa (Boehringer Ingelheim)</td>
<td>Direct thrombin inhibitor</td>
<td>150 mg bid¹,²</td>
<td>314.70</td>
</tr>
<tr>
<td>Apixaban – Eliquis (BMS)</td>
<td>Direct factor Xa inhibitor</td>
<td>5 mg bid³</td>
<td>315.00</td>
</tr>
<tr>
<td>Edoxaban – Savaysa (Daichi Sankyo)</td>
<td>Direct factor Xa inhibitor</td>
<td>60 mg once/d⁴</td>
<td>277.20</td>
</tr>
<tr>
<td>Rivaroxaban – Xarelto (Janssen)</td>
<td>Direct factor Xa inhibitor</td>
<td>20 mg once/d⁵</td>
<td>314.70</td>
</tr>
</tbody>
</table>

1. Approximate WAC for 30 days’ treatment at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. May 3, 2015. Reprinted with permission from First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy.

2. Coadministered with a parenteral coagulant for ≤5 days and until INR is in therapeutic range (2-3) for ≥24 hours.

3. After 5-10 days of parenteral anticoagulation for VTE.

4. Dosage is 75 mg bid for atrial fibrillation in patients with CrCl 15-30 mL/min, according to US labeling. The American College of Chest Physicians and Health Canada do not recommend use for atrial fibrillation in patients with CrCl <30 mL/min. Not studied for VTE in patients with CrCl <30 mL/min. Avoid use with P-glycoprotein inhibitors for atrial fibrillation in patients with CrCl <30 mL/min and for VTE in patients with CrCl <50 mL/min. Avoid use with P-glycoprotein inhibitors for atrial fibrillation in patients with CrCl <50 mL/min.

5. Dosage is 10 mg bid for first 7 days for VTE. Dosage is 2.5 mg bid for atrial fibrillation in patients with ≥2 of the following: age ≥80 years, weight ≥60 kg, serum creatinine ≥1.5 mg/dL. In patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein, reduce the dosage of apixaban by 50% to a minimum of 2.5 mg bid, or avoid coadministration in patients already taking 2.5 mg bid.

6. Do not use for atrial fibrillation in patients with CrCl <95 mL/min. Dosage is 30 mg once/d in patients with CrCl 15-50 mL/min, or in patients being treated for VTE who weigh ≤60 kg or are concomitantly taking certain P-glycoprotein inhibitors.

7. Dosage is 15 mg bid for first 21 days for VTE. Dosage is 15 mg once/d for atrial fibrillation in patients with CrCl 15-50 mL/min. Taken with the evening meal for atrial fibrillation and with food for VTE.

no fatal intracranial bleeds in the edoxaban group compared to six in warfarin-treated patients. More than 90% of the study population had a CrCl >50 mL/min, and renal function had no effect on the incidence of the primary endpoint in patients taking edoxaban.⁸

Atrial Fibrillation — In a randomized, double-blind trial (ENGAGE AF-TIMI 48) in 21,105 patients with atrial fibrillation and a CHADS₂ score ≥2, stroke or systemic embolism (the primary endpoint) occurred after a median follow-up of 2.8 years at a significantly lower annual rate with edoxaban than with warfarin (1.18% vs. 1.50%). Edoxaban use was also associated with significantly reduced annual rates of major bleeding (2.75% vs. 3.43%), intracranial bleeding (0.39% vs. 0.85%), and cardiovascular death (2.74% vs. 3.17%).⁹

Among patients with CrCl >95 mL/min, however, the rate of ischemic stroke was significantly higher with edoxaban (0.9%) than with warfarin (0.4%).¹⁰

ADVERSE EFFECTS — The most common adverse effect of edoxaban in clinical trials was bleeding. Edoxaban has no established antidote to reverse its anticoagulant effect, which persists for about 24 hours after the last dose, and it is not dialyzable. Epidural or spinal hematomas resulting in permanent paralysis could occur in patients taking the drug who require neuraxial anesthesia or spinal puncture.

PREGNANCY — Edoxaban is classified as category C (no teratogenic effects in animals, no adequate studies in women) for use during pregnancy.

DRUG INTERACTIONS — Concomitant use of edoxaban with other drugs that interfere with hemostasis, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs), increases the risk of bleeding.

Edoxaban is a substrate of P-glycoprotein (P-gp) and should not be used concomitantly with the P-gp inducer rifampin. Concomitant use of P-gp inhibitors may increase serum concentrations of edoxaban.¹¹

DOSE ADJUSTMENTS — Dosage adjustments for edoxaban and the other oral anticoagulants are listed in Table 2.

Subgroup analyses of the Hokusai-VTE trial, described in FDA review documents, found that patients treated for VTE with edoxaban 30 mg/day because they weighed ≤60 kg had similar efficacy and safety outcomes as those receiving 60 mg/day who did not require a dosage adjustment. An analysis of patients taking edoxaban 30 mg/day solely because of concomitant P-gp inhibitor use was not possible because this subgroup constituted <1% of the study population. Current product labeling recommends that patients with VTE who are receiving a P-gp inhibitor specified in the Hokusai-VTE trial protocol (verapamil or quinidine for chronic use, or azithromycin, clarithromycin, erythromycin, ketoconazole, oritraconazole for acute use) take 30 mg/day of edoxaban.

Subgroup analyses of the ENGAGE AF-TIMI 48 trial, described in FDA review documents, found that patients with atrial fibrillation taking 30 mg/day of edoxaban because they weighed ≤60 kg or were taking a P-gp inhibitor had a smaller reduction in the incidence of the primary endpoint than those receiving
60 mg/day who did not require a dosage adjustment. Consequently, no dose reduction is recommended for patients with atrial fibrillation based on body weight or concomitant use of a P-gp inhibitor. Edoxaban should not be used for treatment of atrial fibrillation in patients with a CrCl >95 mL/min.

CONCLUSION — Edoxaban (Savaysa) appears to be similar in efficacy to warfarin in treating acute venous thromboembolism. For prevention of stroke in patients with nonvalvular atrial fibrillation, edoxaban was at least as effective as warfarin and caused less bleeding, but in patients with a CrCl >95 mL/min, the incidence of ischemic stroke was higher with edoxaban, and the drug should not be used in such patients. How edoxaban compares in efficacy and safety with dabigatran (Pradaxa), rivaroxaban (Xarelto), or apixaban (Eliquis) remains to be determined.