

FDA approves anti-clotting drug *Edoxaban* (Savaysa®) to treat atrial fibrillation, Deep Vein Thrombosis, and Pulmonary Embolism

Atrial fibrillation is one of the most common types of abnormal heart rhythm. It occurs when the heart's two upper chambers (atria) do not contract properly, allowing blood clots to form, which can break off and travel to the brain or other parts of the body. Patients with atrial fibrillation experience an abnormal, irregular and rapid heartbeat.(1)

Edoxaban (Savaysa®) also has been approved to treat **Deep Vein Thrombosis (DVT)** and **Pulmonary Embolism (PE)** in patients who have already been treated with an anti-clotting drug administered by injection or infusion (parenterally), for five to ten days.(3)

On **January 8, 2015** U.S. Food and Drug Administration announced the approval of a new anti-clotting drug called *Edoxaban* (Savaysa®) as a tablet to reduce the risk of stroke and dangerous blood clots (systemic embolism) in patients with atrial fibrillation that is not caused by a heart valve problem.(3)

Edoxaban (Savaysa®) is an anti-clotting drug manufactured by **Daiichi Sankyo Co., Ltd.** *Edoxaban* (Savaysa®) works by inhibiting the free factor Xa selectively and prothrombinase activity and inhibits thrombin-induced platelet aggregation. The Inhibition of factor Xa in the coagulation cascade reduces thrombin generation and thrombus formation, which prevent the clot formation. (2)

On **Jan 8, 2014** Daiichi Sankyo Co., Ltd. Submitted *Edoxaban* (Savaysa®) New Drug Application (NDA) to the U.S. FDA. The NDA submission 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 atrial fibrillation (AF) or VTE. The global *Edoxaban* clinical trial program includes two phase 3 clinical studies, Hokusai-VTE and ENGAGE AF-TIMI 48 (Effective aNticoaGulation with Factor XA Next GEneration in Atrial Fibrillation) which are the largest comparative trials of a novel oral anticoagulant in these patient populations, involving 8,292 and 21,105 patients, respectively. Forming the basis of the NDA for *Edoxaban* for the prevention of stroke, as well as for the treatment of DVT or PE and for prevention of recurrence of symptomatic VTE. (4)

ENGAGE AF-TIMI 48 a phase 3 multinational, double-blind, double-dummy, non-inferiority trial that enrolled 21,105 patients with AF at moderate-to-high risk of stroke to once-daily *Edoxaban* vs. *Warfarin* was conducted on 16 February 2015 to assess the effect of *Edoxaban* vs. *Warfarin* in vitamin K antagonist(VKA) experienced and naive patients with atrial fibrillation. Higher-dose *Edoxaban* significantly reduced the risk of stroke or systemic embolic events (SEE) in patients who were VKA naive [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.56–0.90] and was similar to *Warfarin* in the VKA experienced (HR 1.01, 95% CI 0.82–1.24; *P* interaction = 0.028). Lower-dose *Edoxaban* was similar to *Warfarin* for stroke or SEE prevention in patients who were VKA naive (HR 0.92, 95% CI 0.73–1.15), but was inferior to *Warfarin* in those who were VKA experienced (HR 1.31, 95% 1.08–1.60; *P* interaction = 0.019).

Both higher-dose and lower-dose *Edoxaban* regimens significantly reduced the risk of major bleeding regardless of prior VKA experience (P interaction = 0.90 and 0.71, respectively). And came up with the conclusion that in patients with AF, *Edoxaban* appeared to demonstrate greater efficacy compared with *Warfarin* in patients who were VKA naive than VKA experienced. And *Edoxaban* significantly reduced major bleeding compared with *Warfarin* regardless of prior VKA exposure.(5)

Hokusai-VTE Trial a randomized, double-blind, noninferiority study, that was conducted to assess the efficacy of *Edoxaban* in the treatment of symptomatic venous thromboembolism compared to *Warfarin*, and enrolled 8,292 patients among which 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism, and had initially received heparin, patients received *Edoxaban* or *Warfarin*. Among patients receiving *Warfarin*, the time in the therapeutic range was 63.5%. *Edoxaban* was noninferior 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%) (Hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; $P < 0.001$ for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the *Edoxaban* group and 423 patients (10.3%) in the *Warfarin* group (hazard ratio, 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 pulmonary embolism had right ventricular dysfunction, as assessed by measurement of N-terminal pro-brain natriuretic peptide levels; the rate of recurrent venous thromboembolism in this subgroup was 3.3% in the *Edoxaban* group and 6.2% in the *Warfarin* group (hazard ratio, 0.52; 95% CI, 0.28 to 0.98). The study concluded that *Edoxaban* administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism.(7)

On December 2014, **The STARS E-3 Trial** a phase 3 trial compared the safety and efficacy of *Edoxaban*, with *Enoxaparin* for thromboprophylaxis after total knee arthroplasty (TKA) in patients in Japan and Taiwan. Of 716 patients enrolled, 360 and 356 were randomized to receive *Edoxaban* or *Enoxaparin*, respectively. The primary efficacy endpoint of the study was the composite of symptomatic pulmonary embolism and symptomatic and asymptomatic deep vein thrombosis, and it occurred in 22/299 (7.4%) and 41/295 (13.9%) patients in the *Edoxaban* and *Enoxaparin* groups, respectively (relative risk reduction = 46.8%), indicating non-inferiority and superiority of *Edoxaban* versus *Enoxaparin*. In the *Edoxaban* and *Enoxaparin* groups, major bleeding occurred in 4/354 (1.1%) versus 1/349 (0.3%) patients; major or Clinically Relevant Non-Major Bleeding (CRNM) bleeding occurred in 22/354 (6.2%) versus 13/349 (3.7%) patients, respectively. Indicating that *Edoxaban* was more effective for thromboprophylaxis than subcutaneous *Enoxaparin* following TKA and demonstrated a similar incidence of bleeding events.(6)

Taking into account the clinical evidence and data up to date *Edoxaban* hold promise as an important addition to other anti-clotting drugs as future role player and treatment option for thrombotic events management. However, more studies and clinical trials are needed to assess safety, efficacy and its exact position in the thrombotic events management guidelines.

Resources:

1. Deep Vein Thrombosis Health Center,
Available at: <http://www.webmd.com/dvt/blood-clots>
Last accessed on 24/2/2015.
2. Edoxaban monograph:
Available at:
http://online.lexi.com/lco/action/doc/retrieve/docid/multinat_f/5488128#pha
Last accessed on 24/2/2015.
3. FDA approves anti-clotting drug Savaysa Newsletter,
Available at:
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm429523.htm>
Last accessed on 24/2/2015.
4. NDA Submitted for Savaysa:
Available at: http://www.drugs.com/nda/savaysa_140108.html
Last accessed on 24/2/2015.
5. Michelle L. O'Donoghue , Christian T,etal. “Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation”. *The European Heart Journal*. 2015;
<http://dx.doi.org/10.1093/eurheartj/ehv014> First published online: 16 February 2015.
6. Takeshi Fuji, Ching-Jen Wang,Satoru Fujita,etal. “Safety and Efficacy of Edoxaban, an Oral Factor Xa Inhibitor, Versus Enoxaparin for Thromboprophylaxis After Total Knee Arthroplasty: The STARS E-3 Trial”. *Thrombosis Research Journal*. 2014;134:1198–1204.
7. Harry R. Büller, Hervé Décousus, Michael A,etal.” Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism”. *The New England Journal of Medicine*. 2013; 369:1406-1415.

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