

## Press Release

# **Daiichi Sankyo's Once-Daily Lixiana® (edoxaban) Receives Positive CHMP Opinion for the Prevention of Stroke and Systemic Embolism in Non-Valvular Atrial Fibrillation and for the Treatment and Prevention of Recurrent Venous Thromboembolism in Europe**

- *The European Committee for Medicinal Products for Human Use recommended approval of once-daily Lixiana®*
- *The positive opinion is based on data from the ENGAGE AF-TIMI 48 and Hokusai-VTE studies, the largest single comparative global trials of a novel oral anticoagulant in patients with non-valvular atrial fibrillation or venous thromboembolism, involving 21,105 and 8,292 patients, respectively*
- *Daiichi Sankyo looks forward to receiving approval decision by the European Commission soon, which is the basis for marketing authorisation in all European Union member states*

**Tokyo, Japan (April 27, 2015)** – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that the European Committee for Medicinal Products for Human Use (CHMP) has recommended approval of Lixiana® (edoxaban), an oral, once-daily selective factor Xa inhibitor, for the prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAf) with one or more risk factors. The CHMP also recommended approval of Lixiana for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. The two related conditions DVT and PE are collectively referred to as venous thromboembolism (VTE).<sup>1</sup>

“The CHMP recommendation to approve once-daily edoxaban for the NVAf and VTE indications is an important milestone for our company,” said Glenn Gormley, MD, PhD, Senior Executive Officer and Global Head of R&D, Daiichi Sankyo Company, Limited and Executive Chairman and President, Daiichi Sankyo, Inc. “The European regulatory committee has recognised the positive benefit-risk profile of the 60 mg dosing regimen [with a dose reduction to 30 mg in selected patients with creatinine clearance (CrCL) 15-50 mL/min, body weight ≤ 60 kg, or concomitant use of certain P-glycoprotein (P-gp) inhibitors].”

## Press Release

The CHMP opinion to approve once-daily edoxaban for the prevention of stroke and SE in adult patients with NVAF with one or more risk factors and for the treatment and prevention of recurrent VTE (DVT and PE) is based on the data of the phase 3 ENGAGE AF-TIMI 48 and Hokusai-VTE studies, respectively.<sup>2,3</sup>

In the ENGAGE AF-TIMI 48 study, once-daily edoxaban 60 mg demonstrated non-inferiority to well-managed warfarin for the primary efficacy endpoint of occurrence of stroke or SE in patients with NVAF (1.18% vs. 1.50% per year, respectively; hazard ratio [HR], 0.79; 97.5% confidence interval [CI], 0.63 to 0.99,  $p < 0.001$ ). In addition, once-daily edoxaban 60 mg demonstrated a significant 20% risk reduction of major bleeding in patients with NVAF compared to warfarin (2.75% vs. 3.43% per year, respectively; HR, 0.80; 95% CI, 0.71 to 0.91,  $p < 0.001$ ).<sup>2</sup>

In the Hokusai-VTE study, once-daily edoxaban 60 mg was non-inferior to warfarin for the primary efficacy endpoint of recurrence of symptomatic VTE (3.2% vs. 3.5% of patients, respectively; HR, 0.89; 95% CI, 0.70 to 1.13,  $p < 0.001$ ). In addition, edoxaban demonstrated a significant 19% risk reduction of clinically relevant bleeding in patients with VTE compared to warfarin (8.5% vs. 10.3% of patients, respectively; HR, 0.81; 95% CI, 0.71 to 0.94,  $p = 0.004$ ).<sup>3</sup>

Atrial fibrillation (AF) is the most common type of heart rhythm disorder, and is associated with substantial morbidity and mortality.<sup>4</sup> More than six million Europeans suffer from AF and this figure is expected to at least double over the next 50 years.<sup>5,6</sup> One in five of all strokes is as a result of AF.<sup>5</sup>

VTE is a major cause of morbidity and mortality.<sup>7</sup> VTE is a major health problem in Europe, with more than one million VTE events or deaths per year (France, Germany, Italy, Spain, Sweden, UK), including more than 370,000 VTE-related deaths.<sup>7</sup>

### About the ENGAGE AF-TIMI 48 Study

ENGAGE AF-TIMI 48 (Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation) was a three-arm, randomized, double-blind, double-dummy, global phase 3 clinical trial comparing once-daily edoxaban with well-managed warfarin in 21,105 patients with NVAF at moderate-to-high risk of thromboembolic events at 1,393 centers in 46 countries. ENGAGE AF-TIMI 48 compared two edoxaban treatment strategies, a higher dose arm (60 mg or 30 mg dose reduced) once-daily and a

## Press Release

lower dose arm (30 mg or 15 mg dose reduced) once-daily, with warfarin in patients with NVAf for a median of 2.8 years follow-up. Patients were dose reduced for CrCL 30 to 50 mL/min, body weight of 60 kg or less or certain P-gp inhibitor use. ENGAGE AF-TIMI 48 represents the largest and longest single comparative global trial with a novel anticoagulant in patients with NVAf performed to date.<sup>2</sup> The full results were presented at the AHA Scientific Sessions 2013 in Dallas and published in the *New England Journal of Medicine*.

### About the Hokusai-VTE Study

Hokusai-VTE was a global, event-driven, randomized, double-blind, double-dummy, parallel-group phase 3 clinical study involving 8,292 patients in 439 clinical sites across 37 countries to evaluate once-daily edoxaban in patients with either acute symptomatic DVT, PE or both. The Hokusai-VTE study was designed to reflect clinical practice using a flexible treatment duration of 3-12 months in a broad spectrum of VTE patients, including initial use of parenteral anticoagulant (heparin) for 5-10 days, the proven global standard of care. Patients were randomized to receive edoxaban 60 mg once-daily (dose reduced to 30 mg for CrCL 30 to 50 mL/min, body weight of 60 kg or less, or certain P-gp inhibitor use) or the comparator, warfarin, following initial open-label enoxaparin or unfractionated heparin therapy. In the comparator arm, patients received initial heparin therapy concurrently with warfarin, titrated to a target INR of 2.0 to 3.0, followed by warfarin alone. The treatment duration was from 3 months and up to a maximum of one year. The duration of study treatment was determined by the investigator based on the patient's clinical features.<sup>3</sup> The full results were presented at the ESC Congress 2013 in Amsterdam and published in the *New England Journal of Medicine*.

### About Edoxaban

Edoxaban is an investigational, oral, once-daily anticoagulant that specifically inhibits factor Xa, which is an important factor in the coagulation system that leads to blood clotting.<sup>8</sup> The global edoxaban clinical trial program includes two phase 3 clinical studies, Hokusai-VTE and ENGAGE AF-TIMI 48, which included nearly 30,000 patients combined. The results from these trials form the basis of regulatory filings for edoxaban for symptomatic VTE in patients with DVT and/or PE, and for the prevention of stroke and SE in NVAf, respectively.<sup>2,3</sup>

Edoxaban is currently marketed in Japan and the U.S. and has received approval in Switzerland.<sup>9,10,11</sup> In other countries, regulatory review is ongoing.

## Press Release

### About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, dyslipidemia and bacterial infections used by patients around the world, the Group has also launched treatments for thrombotic disorders and is building new product franchises. Furthermore, Daiichi Sankyo research and development is focused on bringing forth novel therapies in oncology and cardiovascular-metabolic diseases, including biologics. The Daiichi Sankyo Group has created a “Hybrid Business Model,” to respond to market and customer diversity and optimize growth opportunities across the value chain. For more information, please visit: [www.daiichisankyo.com](http://www.daiichisankyo.com).

### Contact

Daria Munsel (Europe)  
Daiichi Sankyo Europe GmbH  
Edoxaban Comm. & Product PR Europe  
+49 (89) 7808728

Yasuki Minobe (Global)  
Daiichi Sankyo Group  
Corporate Communication Department  
+81 (3) 62251126

### Forward-looking statements

This press release contains forward-looking statements and information about future developments in the sector, and the legal and business conditions of DAIICHI SANKYO Co., Ltd. Such forward-looking statements are uncertain and are subject at all times to the risks of change, particularly to the usual risks faced by a global pharmaceutical company, including the impact of the prices for products and raw materials, medication safety, changes in exchange rates, government regulations, employee relations, taxes, political instability and terrorism as well as the results of independent demands and governmental inquiries that affect the affairs of the company. All forward-looking statements contained in this release hold true as of the date of publication. They do not represent any guarantee of future performance. Actual events and developments could differ materially from the forward-looking statements that are explicitly expressed or implied in these statements. DAIICHI SANKYO Co., Ltd. assume no responsibility for the updating of such forward-looking statements about future developments of the sector, legal and business conditions and the company.

## References

1. Centers for Disease Control and Prevention. Deep Vein Thrombosis & Pulmonary Embolism. Available at: <http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/deep-vein-thrombosis-and-pulmonary-embolism>. [Last accessed: April 2015].
2. Giugliano R, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
3. Büller H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.
4. Iqbal MB, et al. Recent developments in atrial fibrillation. *BMJ*. 2005;330(7485):238-43.
5. Camm A, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-429.
6. Krijthe BP, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34(35):2746-2751.
7. Cohen A, et al. Venous thromboembolism (VTE) in Europe. *Thromb Haemost*. 2007;98(4):756-764.
8. Ogata K, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol*. 2010;50(7):743-753.
9. Daiichi Sankyo press release - Daiichi Sankyo Launches New Formulation of LIXIANA® 60 mg Tablets (edoxaban) in Japan. 8 Dec 2014. Available at: [http://www.daiichisankyo.com/media\\_investors/media\\_relations/press\\_releases/detail/006226.html](http://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006226.html). [Last accessed: April 2015].
10. Daiichi Sankyo press release - SAVAYSA™ (edoxaban) Now Available in U.S. Pharmacies. 9 February 2015. Available at: [http://www.daiichisankyo.com/media\\_investors/media\\_relations/press\\_releases/detail/006247.html](http://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006247.html). [Last accessed: April 2015].
11. Daiichi Sankyo press release - Daiichi Sankyo's Once-Daily LIXIANA® (edoxaban) Approved for the Prevention of Stroke and Systemic Embolism in Non-Valvular Atrial Fibrillation and for the Treatment and Prevention of Recurrent Venous Thromboembolism in Switzerland. 15 April 2015. Available at: [http://www.daiichisankyo.com/media\\_investors/media\\_relations/press\\_releases/detail/006269.html](http://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006269.html). [Last accessed: April 2015].