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U.S. FDA Approves Daiichi Sankyo's Once-Daily SAVAYSA™ (edoxaban) Tablets for Reduction of Stroke Risk in Non-Valvular Atrial Fibrillation and for the Treatment of Venous Thromboembolism

- *U.S. approvals for SAVAYSA based on data from the ENGAGE AF-TIMI 48 and Hokusai-VTE studies, the largest and longest single comparative global trials of a novel oral anticoagulant in patients with NVAF or VTE, involving 21,105 and 8,292 patients, respectively*
- *SAVAYSA expected to be commercially available in the U.S. in February 2015*
- *FDA approvals follow September 2014 approval in Japan for NVAF and VTE indications*

Tokyo, Japan (January 9, 2015) and Parsippany, NJ (January 8, 2015) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that the U.S. Food and Drug Administration (FDA) has approved SAVAYSA™ (edoxaban) Tablets, an oral, once-daily selective factor Xa-inhibitor, to reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF). In ENGAGE AF-TIMI 48, SAVAYSA was non-inferior to warfarin in the overall study population for the primary efficacy endpoint of stroke or SE. As stated in the U.S. label, SAVAYSA should not be used in NVAF patients with creatinine clearance (CrCL) levels greater than 95 mL/min because in that population there is an increased risk of ischemic stroke compared to warfarin. Patients with CrCL less than or equal to 95 mL/min represented 77% of the patients studied. In those patients, SAVAYSA 60 mg (30 mg dose reduced) reduced the risk of stroke and SE when compared to warfarin (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.55 to 0.84), and the rates of cardiovascular death with SAVAYSA and warfarin were 2.95% per year vs. 3.59% per year, respectively.¹ The FDA also approved SAVAYSA for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant.

“The approval of SAVAYSA demonstrates our commitment to providing new treatment options for cardiovascular diseases with significant unmet needs and reinforces our leadership in factor Xa-inhibition research, which began more than 30 years ago,” said Joji Nakayama, Representative Director, President and Chief Executive Officer, Daiichi Sankyo Company, Limited. “We look



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forward to making SAVAYSA available to patients in the U.S. with NVAF and venous thromboembolism, two serious conditions that are expected to double in prevalence by mid-century.”

“SAVAYSA is an important new anticoagulant in the U.S. and in the ENGAGE AF-TIMI 48 trial, SAVAYSA has been shown to reduce the risk of stroke and SE with significantly less major bleeding for patients with NVAF, and in the Hokusai-VTE trial, to treat DVT and PE with significantly less clinically relevant bleeding versus warfarin, the most commonly prescribed anticoagulant,” 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. “In addition, SAVAYSA offers the convenience of once-daily dosing, no need for routine blood monitoring and the flexibility to be taken with or without a meal.”

The approved indications in the U.S. for SAVAYSA are based on data from the ENGAGE AF-TIMI 48 and Hokusai-VTE studies. The most common side effects observed in clinical trial participants were bleeding and anemia.^{1,2} SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding.

In ENGAGE AF-TIMI 48, SAVAYSA had significantly less major bleeding in patients with NVAF, both in the overall study population (HR, 0.80; 95% CI, 0.70 to 0.91, $p < 0.001$) and in patients with CrCL less than or equal to 95 mL/min (HR, 0.84; 95% CI, 0.73 to 0.97). In addition, in the approved population, there were lower rates of intracranial hemorrhage with SAVAYSA compared to warfarin in patients with NVAF (0.5% vs. 1.0% per year, respectively; HR, 0.44, 95% CI, 0.32 to 0.61). In ENGAGE AF-TIMI 48, there was a significant increase in gastrointestinal bleeding events in the approved population compared to warfarin of 1.8% vs. 1.3% per year, respectively (HR, 1.4; 95% CI, 1.13 to 1.73).¹

In the overall Hokusai-VTE study population, once-daily SAVAYSA 60 mg was non-inferior to warfarin for the primary efficacy endpoint of recurrence of symptomatic venous thromboembolism (VTE) (3.2% vs. 3.5%, respectively; HR, 0.89; 95% CI, 0.70 to 1.13). In addition, SAVAYSA demonstrated a significant 19% lower rate of clinically relevant bleeding in patients with VTE compared to warfarin (8.5% vs. 10.3%, respectively; HR, 0.81; 95% CI, 0.71 to 0.94, $p = 0.004$).²



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Important Safety Information About SAVAYSA™ (edoxaban) Tablets

BOXED WARNINGS:

- **REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CrCL > 95 ML/MIN**

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once-daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.

- **PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS**

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance in the Prescribing Information.

- **SPINAL/EPIDURAL HEMATOMA**

- Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.
- Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; a history of spinal deformity or spinal surgery.
- Optimal timing between the administration of SAVAYSA and neuraxial procedures is not known.
- Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits



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and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

SAVAYSA is contraindicated in patients with active pathological bleeding.

WARNINGS AND PRECAUTIONS

Bleeding Risk

SAVAYSA increases the risk of bleeding and can cause serious, potentially fatal, bleeding. Promptly evaluate any signs or symptoms of blood loss. Discontinue SAVAYSA in patients with active pathological bleeding. There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance.

Mechanical Heart Valves or Moderate to Severe Mitral Stenosis

The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. SAVAYSA is not recommended in these patients.

ADVERSE REACTIONS

- **NVAF:** The most common adverse reactions ($\geq 5\%$) are bleeding and anemia.
- **DVT/PE:** The most common adverse reactions ($\geq 1\%$) are bleeding, rash, abnormal liver function tests and anemia.

DISCONTINUATION FOR SURGERY AND OTHER INTERVENTIONS

Hold SAVAYSA at least 24 hours before invasive or surgical procedures because of the risk of bleeding. SAVAYSA can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established.



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DRUG INTERACTIONS

- **Anticoagulants, Antiplatelets and Thrombolytics:** Coadministration of anticoagulants, antiplatelets and thrombolytics may increase the risk of bleeding.
- **P-gp Inducers:** Avoid concomitant use of SAVAYSA with rifampin.

SPECIAL POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing.
- Impaired renal function (CrCL 15 to 50 mL/min): Reduce SAVAYSA dose to 30 mg.
- Moderate or severe hepatic impairment: Not recommended.
- Pregnancy Category C.

Please see full [Prescribing Information](#), including Boxed WARNINGS and Medication Guide.

INDICATIONS

Savaysa™ (edoxaban) is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAf). SAVAYSA should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin.

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant.

Dosing and Administration for SAVAYSA (edoxaban) Tablets

Reduction of Stroke and SE in NVAf: The recommended dose of SAVAYSA is 60 mg taken orally once daily. Creatinine clearance should be assessed before initiating therapy with SAVAYSA.

SAVAYSA should not be used in patients with CrCL > 95 mL/min. The dose of SAVAYSA should be reduced to 30 mg once daily in patients with CrCL 15 to 50 mL/min.

Treatment of DVT and PE: The recommended dose of SAVAYSA is 60 mg taken orally once daily following 5-10 days of initial therapy with a parenteral anticoagulant. The recommended dose of SAVAYSA is 30 mg taken once daily following initial use of 5-10 days of heparin for patients who have CrCL between 30 mL/min and 50 mL/min, patients who weigh less than or equal to 60 kg and patients who are on concomitant p-glycoprotein inhibitors.



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Global Clinical Trial Program for Edoxaban

Edoxaban is an oral, once-daily anticoagulant that selectively inhibits factor Xa, which is an important factor in the coagulation system that leads to blood clotting.³ The global 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 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 reduction in the risk of stroke in NVAF, respectively.^{1,2} Edoxaban is currently under regulatory review around the world for these indications, including in the EU.

On September 26, 2014, Daiichi Sankyo announced that it received approval from the Ministry of Health, Labour and Welfare in Japan for LIXIANA[®] (JAN: Edoxaban Tosilate Hydrate, INN: edoxaban) for the prevention of ischemic stroke and SE in patients with NVAF and for the treatment and recurrence prevention of VTE [DVT and pulmonary thromboembolism].⁴

Edoxaban was approved in Japan in April 2011 for the prevention of VTE after major orthopedic surgery and was launched in July 2011.⁵

About the ENGAGE AF-TIMI 48 Trial

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 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 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. Patients were dose reduced for creatinine clearance 30 to 50 mL/min, body weight less than 60 kg or certain p-glycoprotein inhibitor use. The lower dose arm (30 mg or 15 dose reduced) is not an approved treatment regimen in the U.S. ENGAGE AF-TIMI 48 represents the largest and longest single comparative global trial of a novel anticoagulant in patients with NVAF performed to date.¹ The full results were presented at the AHA Scientific Sessions 2013 in Dallas and published in the *New England Journal of Medicine*.



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About the Hokusai-VTE Trial

Hokusai-VTE was a global, event-driven, randomized, double-blind, 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, including initial use of parenteral anticoagulant (heparin) for 5-10 days, the proven global standard of care, in both arms, in a broad spectrum of VTE patients. Following treatment with open-label enoxaparin or unfractionated heparin for at least five days, and either warfarin or placebo (administered to edoxaban group), patients were randomized to receive either edoxaban 60 mg (patients were dose reduced to 30 mg for CrCL 30 to 50 mL/min, body weight less than 60 kg or certain p-glycoprotein inhibitor use) or warfarin for at least three months and up to a maximum of one year (duration of study treatment was determined by the investigator based on the patient's clinical features).² The full results were presented at the ESC Congress 2013 in Amsterdam and published in the *New England Journal of Medicine*.

About Atrial Fibrillation

AF is a condition in which the heartbeat is irregular, and can potentially lead to a stroke.⁶ AF is a common condition, affecting approximately 2.3-3.4% of people in developed nations.⁷ AF affects approximately 6.1 million people in the U.S.⁸ The incidence of AF increases with age, with a prevalence of 2.3% and 5.9% in people older than 40 and 65 years, respectively.^{9,10} Approximately 70% of individuals with AF are between 65 and 85 years of age.¹¹ Stroke due to all causes is the fourth most common cause of death in the U.S., responsible for approximately 200,000 deaths each year.¹² Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.¹¹ Strokes due to AF are nearly twice as likely to be fatal than strokes in patients without AF at 30 days and have poorer prognosis than non-AF related strokes, with a 50% increased risk of remaining disabled at three months.^{12,13}

About Venous Thromboembolism

VTE is an umbrella term for two conditions, DVT and PE. DVT is a disease caused by a blood clot found in deep veins, usually within the lower leg, thigh or pelvis, although they can occur in other parts of the body as well.¹⁴ PE occurs when part of a clot detaches and lodges in the pulmonary arteries, causing a potentially fatal condition.¹⁵ In the U.S., it is currently estimated that more than 950,000 VTE events and approximately 300,000 VTE related deaths occur each year.^{16,17}



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Approximately 30% of people with VTE die within one month of diagnosis and about 20% of those with PE experience sudden death.¹⁸

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.

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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.

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