PRESS RELEASE
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Once-Daily Oral Anticoagulant LIXIANA® (edoxaban) Met Primary Endpoint in Investigational Hokusai-VTE CANCER Study

- *Hokusai-VTE CANCER study is a phase 3b, prospective, randomized, open-label, blind end-point (PROBE) study evaluating edoxaban versus low molecular weight heparin (LMWH) dalteparin in venous thromboembolism (VTE) associated with primarily active cancer*[1,2,3]
- *Study met primary endpoint of non-inferiority in the recurrence of VTE or ISTH-defined major bleeding*[1,2,3]

Laval, Québec (December 15, 2017) – Servier Canada today announced results from the Hokusai-VTE CANCER study evaluating oral edoxaban (known by the brand names LIXIANA® in Canada and outside the U.S. and SAVAYSA® in the U.S.), and found that edoxaban is non-inferior to subcutaneous injectable LMWH dalteparin for the treatment of cancer-associated VTE or major bleeding[2,3]. The results of the study were simultaneously published in the *New England Journal of Medicine* (NEJM) and presented during the late-breaker session at the 59th American Society of Hematology (ASH) Annual Meeting in Atlanta, Georgia.

The Hokusai-VTE CANCER study met the primary objective of non-inferiority of edoxaban for the composite outcome of first recurrent VTE or ISTH-defined major bleeding during a 12-month study period, which occurred in 67 of 522 patients (12.8%) in the edoxaban group compared with 71 of 524 patients (13.5%) in the dalteparin group (hazard ratio with edoxaban, 0.97; 95% CI, 0.70 to 1.36; P = 0.006 for non-inferiority) for a risk difference (edoxaban minus dalteparin) of -0.7% (95% CI, -4.8 to 3.4)[2,3]. The difference in risk for recurrent VTE was -3.4% (95% CI, -7.0 to 0.2) whereas the corresponding difference in risk for major bleeding was 2.9% (95% CI, 0.1 to 5.6)[3]. The frequencies of severe major bleeding events

at presentation (categories 3 and 4) were similar during treatment with edoxaban or dalteparin (12 patients in each group, respectively)[2,3]. There was no fatal bleed in the edoxaban group versus two fatal bleedings in the dalteparin arm[2,3].

The study also met the secondary outcome of event-free survival (free of recurrent VTE, major bleeds or death) at 12 months, and rates were similar between edoxaban and dalteparin (55.0% and 56.5%, respectively)[2,3]. The trial was a PROBE design study and included a broad spectrum of patients (n=1,050) with primarily active cancer; (98%), 53% of which had metastatic cancer and 72% of which were receiving cancer therapy at randomization[2,3].

"Cancer patients with venous thromboembolism are at increased risk of both recurrent venous thromboembolism and bleeding compared with patients without cancer. Both of these complications can delay cancer treatment and necessitate hospitalization. Therefore, both are important. This trial shows that oral edoxaban is as effective as the standard of care, subcutaneous dalteparin. Although there is more major bleeding with edoxaban, there is no increase in serious bleeding. Therefore, our cancer patients with venous thromboembolism now have an oral treatment alternative to subcutaneous dalteparin," said member of the executive committee of the HOKUSAI-VTE Cancer trail, Dr Jeffrey Weitz, MD, Professor of Medicine and Biochemistry at McMaster University and Executive Director of the Thrombosis and Atherosclerosis Research Institute in Hamilton, Ontario.

"The HOKUSAI-VTE Cancer trial is the first large randomized trial comparing a DOAC (Edoxaban) to LMWH (dalteparin) for the management of acute cancer-associated thrombosis and provides compelling and impactful evidence for Edoxaban as a new treatment option in the management of this important complication in Canada," said member of the steering management coordinating committee and investigator in the HOKUSAI-VTE Cancer trial, Dr Marc Carrier, MD, Vice Chair of Research for the Department of Medicine, an Associate Professor in the Faculty of Medicine, Department of Medicine and Senior Scientist in the Clinical Epidemiology Program of The Ottawa Hospital Research Institute.

VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the second leading cause of death in cancer patients receiving chemotherapy[4]. The treatment of cancer-associated VTE is challenging because these patients are at increased risk of both recurrent VTE and major bleeding[2]. The occurrence of VTE increases the risk of death 2-6-fold in cancer patients[4] and can interrupt cancer treatment[5].

"Servier Canada is proud to provide Canadian cancer patients suffering from venous thromboembolism with a new oral treatment option to prevent recurrences of VTE. The arrival of oral edoxaban treatment will change the landscape of acute VTE management in cancer patients and contribute to improving their quality of life." said Mr. Frederic Fasano, CEO of Servier Canada

About the Hokusai-VTE CANCER study[6]

Hokusai-VTE CANCER is a multinational, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) study, evaluating the efficacy and safety of once-daily edoxaban compared to dalteparin for the treatment of VTE associated with cancer[1,2,3]. The purpose of the study was to evaluate edoxaban in comparison with dalteparin in preventing the combined outcome of VTE recurrence or major bleeding in patients with VTE associated with cancer[1,2,3]. Other objectives include assessing the effects of treatment on VTE recurrence, clinically relevant bleeding and event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events and death[1,2,3]. The study enrolled 1,050 patients across 13 countries in North America, Europe, Australia and New Zealand[2,3]. Patients were randomized to receive edoxaban 60 mg once-daily (reduced to 30 mg edoxaban for patients with creatinine clearance [CrCL] 30-50 mL/min, body weight ≤ 60 kg, or concomitant use of P-glycoprotein [P-gp] inhibitors), following treatment with LMWH for at least five days; or dalteparin SC 200 IU/kg once-daily for 30 days, then 150 IU/kg once-daily for the remainder of the 12-month study[1,2,3].

About VTE and Cancer

Venous thromboembolism (VTE) is an umbrella term for two conditions, deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a major cause of morbidity and mortality in patients with cancer, with an annual incidence that can be as high as 20 percent depending on the cancer type, background risk and time since diagnosis [7,8]. Patients with cancer have multiple risk factors for VTE and the risk of VTE events increases in patients with cancer receiving chemotherapy[9]. In addition, patients with cancer and VTE have a lower survival rate than those without VTE[9].

About LIXIANA® (edoxaban)

Edoxaban is an oral, once-daily, direct factor Xa inhibitor. Factor Xa is one of the key components responsible for blood clotting, so inhibiting this makes the blood thin and less prone to clotting.

Edoxaban was discovered and developed by Daiichi Sankyo Co., Ltd. On June 27, 2016, Daiichi Sankyo and Servier Canada entered into an agreement whereby Servier Canada would market the oral, once-daily anticoagulant edoxaban in Canada, upon approval by the Canadian health authority.

About Servier Canada

Servier Canada Inc., headquartered in Laval, Quebec, is an affiliate of Servier Group. It is the third largest operation for Servier, and it belongs to the top 20 research-based pharmaceutical companies in Canada. Servier Canada is currently marketing five cardiovascular medicines and is expecting further approvals in other therapeutic areas in the coming months. The mission of Servier Canada is to provide the Canadian medical community and their patients with innovative therapeutic solutions in the following therapeutic areas: cardiovascular, diabetes and oncology. Servier Canada collaborates with various stakeholders including researchers, biotech entrepreneurs and innovators. In addition to these partnerships, the Center of Excellence in Clinical Research of Servier Canada is dedicated to clinical development with more than 50 trials conducted throughout Canada in the last 10 years. More information is available at www.servier.ca

Media relations:
Nadine DOUCET
Servier Canada
(Office) 450-978-9700, ext. 4225
(Cell) 514-601-4881
nadine.doucet@servier.com

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