Servier Canada announces Positive Results of the ENTRUST-AF PCI Study of LIXIANA® (edoxaban) in Patients with Atrial Fibrillation

- *ENTRUST-AF PCI study achieved the primary safety endpoint of non-inferiority in bleeding for edoxaban-based dual therapy compared with VKA-based triple antithrombotic therapy (using a risk-based duration of ASA for at least one month) in AF patients following stent placement*
- *Data presented during ESC Congress 2019 Hot Line Session and simultaneously published in The Lancet*

Laval, Québec (September 3rd, 2019) – Today, Servier Canada announces results from ENTRUST-AF PCI (n=1,506), the first large randomised study to evaluate the efficacy and safety of once-daily edoxaban (brand name as LIXIANA®) plus a P2Y12 inhibitor (antiplatelet agents) against a regimen of vitamin K antagonist (VKA) plus P2Y12 inhibitor and acetyl salicylic acid (ASA) in atrial fibrillation (AF) patients following successful percutaneous coronary intervention (PCI). The study showed the edoxaban-based regimen is non-inferior compared with the VKA-based triple therapy regimen on the composite endpoint of major or clinically-relevant non-major bleeding over 12 months.[1,2] The results were presented in a late-breaking presentation during the Hot Line Session today at ESC Congress 2019 in Paris, France and published in *The Lancet.*

It is estimated that about 20% to 40% of patients with AF also present with coronary artery disease (CAD), a sizeable proportion of whom require revascularization using percutaneous coronary intervention (PCI) and stent implantation.[3] VKA-based triple therapy including a P2Y12 inhibitor and ASA used to be the treatment of choice for these patients, however, triple therapy has been associated with significantly increased risk of bleeding.[4] ENTRUST-AF PCI was a multinational, multicenter, randomised, open-label, blinded outcome evaluation Phase 3b study that evaluated a 12-month antithrombotic regimen of edoxaban 60 mg once-daily in combination with a P2Y12 inhibitor compared to a VKA in combination with a P2Y12 inhibitor and 100 mg of ASA for a risk adapted duration for one to 12 months in patients with AF following successful stent placement for ACS or stable CAD. The primary safety outcome was the composite of major or clinically relevant non-major bleeding, as defined by the International Society of Thrombosis and Haemostasis.[1]

"Since about one of five patients with AF may require PCI over time, clinicians need data about the safety of the anticoagulant therapy options for stroke prevention when such event occurs. The ENTRUST-AF PCI trial shows today that the combination of edoxaban 60 mg daily in combination with a P2Y12 inhibitor is an alternative to the VKA-based triple therapy in patients with AF post-PCI." Said Dr. Jean-Francois Tanguay, Professor of medicine, Desgroseillers-Bérard Research Chair in interventional cardiology, Université de Montréal and Director of the Interventional Cardiology Division at the Montreal Heart Institute.

The ENTRUST-AF PCI study enrolled 1,506 patients with AF following successful stent placement for ACS (51.6%) or stable CAD (48.4%). Patients were randomised to receive once-daily edoxaban (60 mg or 30 mg per dose reduction criteria) plus a P2Y12 inhibitor for 12 months or a VKA in combination with a P2Y12 inhibitor plus 100 mg of ASA. Major or clinically relevant non-major bleeding, the study's primary endpoint, occurred in 128 (17.0%; annualised: 20.7%) patients in the edoxaban group and 152 (20.1%; annualised: 25.6%) patients in the VKA group (HR: 0.83, 95% CI: 0.654-1.047), demonstrating non-inferiority of the edoxaban-based dual therapy for the 12 months post PCI (p=0.001, pre-specific non-inferiority margin=1.2). There was a trend toward less bleeding with edoxaban, though, results did not show statistical superiority (p=0.115).[1] Similar rates of the main efficacy composite outcome of cardiovascular death, stroke, systemic embolic events, spontaneous myocardial infarction, and definite stent thrombosis were observed for the edoxaban-based dual therapy regimen and the VKA-based triple therapy regimen.

In the ENTRUST-AF PCI study, bleeding events were consistent across all commonly applied bleeding definitions (ISTH, TIMI, BARC). Intracranial hemorrhage occurred in four (0.58% per year) of edoxaban-treated patients and nine (1.32% per year) VKA-treated patients. Fatal bleeding occurred in one patient receiving edoxaban and seven patients receiving VKA treatment.

"Lixiana® (edoxaban) is the latest direct oral anticoagulant marketed in Canada, and it is now publicly reimbursed in almost all provinces. These results reinforce the safety profile of Lixiana® in different sub-types of patients suffering from AF, in this case, patients undergoing a successful PCI. Another recent sub-analysis of the 1-Year data of ETNA-AF, the largest and most comprehensive repository of data on the use of a DOAC in real life, confirmed the safety profile of LIXIANA in the elderly/very elderly AF patients " said Frederic Fasano, CEO of Servier Canada.

ENTRUST-AF PCI is one of more than 10 randomised, controlled trials (RCTs), registries and non-randomised clinical studies that comprise the Edoxaban Clinical Research Programme, EDOSURE. More than 100,000 patients worldwide are expected to participate in EDOSURE studies, with the goal of generating new clinical and real-world data regarding edoxaban use in AF and venous thromboembolism populations, providing physicians and patients worldwide with greater treatment confidence.

About ENTRUST-AF PCI

EdoxabaN TReatment VersUS Vitamin K Antagonist in PaTients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF- PCI) is a prospective, multinational, multicenter, randomised, open-label with blinded endpoint evaluation phase 3b study. The ENTRUST-AF PCI trial was designed to evaluate the safety and accrue exploratory information on the efficacy of an edoxaban-based antithrombotic regimen compared to a VKA-based antithrombotic regimen in patients with AF following successful PCI with stent implantation. The primary objective of the ENTRUST-AF PCI trial was to compare the incidence of major or clinically relevant non-major International Society on Thrombosis and Haemostasis (ISTH)-defined bleeding over a 12-month period of an edoxaban-based antithrombotic regimen against a VKA-based regimen. 1,506 patients were enrolled in ENTRUST-AF PCI from 186 clinical sites across Europe and Asia. Participants were randomly allocated in a 1:1 ratio to a 12-month antithrombotic regimen of edoxaban and a P2Y12 inhibitor or to a standard therapy with a vitamin K antagonist (VKA) and P2Y12 inhibitor plus ASA for one to 12 months.[1]

About Atrial Fibrillation

AF is a condition where the heart beats irregularly and rapidly. When this happens, blood can pool and thicken in the chambers of the heart causing an increased risk of blood clots. These blood clots can break off and travel through the blood stream to the brain (or sometimes to another part of the body), where they have the potential to cause a stroke.[5]

AF is the most common type of heart rhythm disorder affecting approximately 350,000 Canadians[6] and is associated with substantial morbidity and mortality.[7] Compared to those without AF, people with the arrhythmia have a 3-5 times higher risk of stroke.[9] One in five of all strokes are a result of AF.[8]

About Edoxaban

Edoxaban is an oral, once-daily, direct factor Xa (pronounced “Ten A”) 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. Edoxaban is currently marketed in more than 30 countries and regions around the world.

About Servier Canada

Servier Canada is an affiliate of the independent French Servier Group governed by a Private Foundation. We, at Servier, are committed to therapeutic progress to serve patient needs. We work assiduously to provide the Canadian medical community and its patients with innovative therapeutic solutions. As such, Servier Canada is partnering with various players in the life science ecosystem including researchers, clinicians, entrepreneurs and innovators. In addition to these research partners, the International Center for Therapeutic Research (ICTR) located in Laval, is dedicated to preclinical and clinical development with more than 50 studies conducted throughout Canada over the last 10 years. More information is available at www.servier.ca

About EDOSURE – Edoxaban Clinical Research Programme

More than 10 studies, more than 100,000 patients worldwide

Daiichi Sankyo, who discovered Edoxaban, is committed to expanding scientific knowledge about this DOAC, as demonstrated through research programmes evaluating its use in a broad range of cardiovascular conditions, patient types and clinical settings in atrial fibrillation (AF) and venous thromboembolism (VTE) designed to further build on the results of the pivotal ENGAGE-AF and Hokusai-VTE studies. More than 100,000 patients worldwide are expected to participate in the edoxaban clinical research programme, EDOSURE, which is comprised of more than 10 RCTs (randomised, controlled trials), registries and non-randomised clinical studies, including completed, ongoing and future research. Our goal is to generate new edoxaban clinical and real-world-data regarding its use in AF and VTE populations, providing physicians and patients worldwide with greater treatment assurance.

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