PRESS RELEASE

New 12-month analysis data from ETNA-AF non-interventional study show low bleeding and intracranial hemorrhage (ICH) rates in frail and elderly AF patients on LIXIANA® (edoxaban) during routine clinical care

- *Newly presented data provide reassurance around edoxaban use in vulnerable populations of frail, elderly and renally impaired patients*
- *Clinician's perception of frailty found to potentially be a better marker of clinical outcomes than age*
- *The global ETNA-AF program, which includes ETNA-AF-Europe, is the largest prospective, non-interventional study investigating a single NOAC to date*

Laval, Canada (31 August 2020) – Servier Canada announces one-year results of four sub-analyses from the European and global ETNA-AF (Edoxaban Treatment in routiNe clinical prActice in patients with nonvalvular Atrial Fibrillation) program, a non-interventional safety study evaluating edoxaban (known by the brand name LIXIANA®) treatment in routine clinical practice in >26,000 patients around the world with atrial fibrillation (AF).[i,ii,iii,iv] New 12-month data from the European and global ETNA-AF registries showed rates of bleeding and intracranial hemorrhage (ICH) were considered low by the authors' assessment in frail and elderly patients in routine clinical care.[i,ii,iii] Findings are available virtually at ESC Congress 2020, the annual meeting of the European Society of Cardiology, 29 August – 01 September, and are part of the largest prospective, non-interventional study program investigating a single non-vitamin K antagonist oral anticoagulant (NOAC) in patients with non-valvular atrial fibrillation (NVAF) to date.

In vulnerable populations such as the elderly, frail and those with renal impairment – a common comorbidity for people with AF – anticoagulation for stroke prevention is often not prescribed due to the risk of bleeding, despite these patients being among those most at risk for ischemic events like stroke.[v] However, outcomes from ETNA-AF reinforce the effectiveness and safety of edoxaban in these populations.

"Elderly and frail patients have been underrepresented in certain AF stroke prevention trials, leaving a lack of evidence to support routine NOAC use in these patients," said Dr Ameet Bakhai, Consultant Cardiologist & Cardiovascular R&D Director Royal Free London NHS Trust, UK. "However, these new data should provide clinicians with some confidence of edoxaban's efficacy and safety profile to reduce the risk of stroke for the elderly and frail AF populations."

ETNA-AF-Europe Registry Outcomes: Frailty and renal function

Anticoagulation presents multiple challenges in patients who are frail, as well as those with both frailty and renal impairment.[v] The first of the two data analyses from the 13,092 patient-wide ETNA-AF-Europe registry, assessed key clinical outcomes and risk scores in frail and elderly patients versus non-frail or younger patients correspondingly.[i] Frailty – commonly defined as those at increased risk of disability, hospitalization, and mortality[vi] – was determined by physician perception.[i]

Results from 1,392 patients, who were considered frail, showed:[i]

- Rates of intracranial hemorrhage (ICH) remained low by the investigators' assessment, regardless of frailty status or age, despite frail patients being four times more likely to suffer mortality and presenting with higher rates of major bleeding compared to the non-frail cohort
- Per year, ICH occurred in 0.15% of patients in the frail cohort, compared to 0.27% of those in the non-frail cohort
- Per year, major bleeding occurred in 2.18% of patients in the frail cohort, compared to 0.95% of those in the non-frail cohort
- Per year, total mortality occurred in 10.43% of patients in the frail cohort, compared to 2.49% of those in the non-frail cohort

In addition, the analysis suggested that clinician's perception of frailty appeared to be a better marker of clinical outcomes than age.[i]

In the second analysis from the ETNA-AF-Europe registry, 13,021 patients with renal impairment were observed to evaluate baseline characteristics and assess follow-up outcomes at one-year.[ii] The presence of AF is linked with a greater risk of developing moderate and severe renal impairment, and clinically, anticoagulation presents multiple challenges in patients with impaired renal function because the pharmacokinetic properties and bioavailability of the treatment are often altered in those patients.[vii,viii] Findings of this analysis indicated that across the three groups, who were categorized according to their creatinine clearance (CrCl) levels, those treated with edoxaban had low rates of ICH and hemorrhagic stroke, by the investigators' assessment, and these results were similar in patients across all groups studied.[ii] Regarding renal function, ICH occurred in 0.18%, 0.32% and 0.17% of patients annually, in the following categories moderate to severe renal disease (CrCl ≤50 mL/min), mild renal disease (CrCl (50–80) mL/min) and normal renal function (CrCl ≥80 mL/min)respectively, while hemorrhagic stroke occurred in 0.04%, 0.17% and 0.10% of patients in the aforementioned groups, respectively.[ii]

Global ETNA-AF: Treatment of elderly patients

Findings from one of two global sub-analyses showed that at 12 months, rates of ICH were consistently low across all age groups, while CV mortality increased numerically with age, but to a lower extent than all-cause mortality.[iii] Additional findings from the global registry, assessing the safety and effectiveness of edoxaban given at the recommended or non-recommended dose in AF patients during one-year observation in routine clinical practice, showed that edoxaban is being prescribed at the label recommended dose in the vast majority of patients, but that

non-recommended edoxaban dosage tends to occur more frequently when the CrCl or body weight was closer to the threshold of dose reduction.[iv]

"AF is common in the elderly population as are comorbidities and higher rates of CV events, including bleeding, which all need to be managed with a great deal of consideration for the challenges they present for both clinicians and patients," said Wolfgang Zierhut MD, Executive Director Medical Affairs and Head Thrombosis and Cardiovascular at Daiichi Sankyo Europe. "These latest data show the consistency of edoxaban treatment in providing benefits to a wide range of patients."

ETNA-AF is one of more than 10 randomized, controlled trials (RCTs), registries and non-randomized clinical studies that comprise the Edoxaban Research Program, EDOSURE.

All of the ETNA-AF non-interventional study data presented at ESC Congress 2020 can be found here.

About ETNA-AF

ETNA-AF (Edoxaban Treatment in routiNe clinical prActice in patients with nonvalvular Atrial Fibrillation) is a global program that combines data from distinct non-interventional studies in Europe, East Asia, and Japan in a single database. A total of more than 28,000 patients will be included in the ETNA-AF registries and followed for two years (patients in Europe will be followed for four years). The primary objective of ETNA-AF is to collect information on the use of edoxaban in routine clinical practice, including the safety and efficacy profile in non-preselected patients with NVAF.[ix,x,xi,xii,xiii]

About AF

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.[xiv]

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

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 the Edoxaban Clinical Research Program

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

Daiichi Sankyo, the company that discovered edoxaban, is committed to expanding scientific knowledge about edoxaban, as demonstrated through research programs 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 Program, which is comprised of more than 10 RCTs (randomized, controlled trials), registries and non-randomized 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.

About Servier Canada

Servier Canada is the Canadian affiliate of Servier Group, an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 149 countries and a total revenue of 4.6 billion euros in 2019, Servier employs 22 000 people worldwide. Entirely independent, the Group reinvests on average 25% of its turnover (excluding generics) every year in research and development and uses all its profits for development. Corporate growth is driven by Servier's constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs. Servier also offers eHealth solutions beyond drug development. Servier has been present in Canada since 1978.

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