Eodoxaban from Japan to the World
From the birth of edoxaban to global application for approval

What is Edoxaban?

Edoxaban, an anticoagulant, is a therapeutic agent for thrombosis created that leverages the strength in the field of thrombosis that has been accumulated by Daiichi Sankyo over its long history. It has been developed as a drug that prevents the clogging of blood in the veins and atrium, where the blood flow is stagnant and that prevents serious diseases, such as pulmonary embolism and ischemic stroke from occurring.

The drug warfarin has been used as a standard anticoagulant for over 50 years. Warfarin is associated with considerable variability in its effect due to interactions with foods and drugs used concomitantly. As a result, it requires patients to undergo routine blood tests and frequent dose adjustments to maintain efficacy while trying to minimize the risk of bleeding events.

Our challenge in the research and development of edoxaban was to develop a drug with less inter-individual variations and a wider therapeutic safety range in order to overcome the main drawbacks of warfarin.

Eodoxaban was approved in Japan in April 2011, for the prevention of VTE after major orthopedic leg surgery, and was launched in July 2011 under the brand name LIXIANA®. The name, edoxaban, derives from Edogawa-ku, where Kasai Research and Development Center of Daiichi Sankyo, the birth place of the drug, is located. The use of “Hokusai” in our trial name, “Hokusai-VTE,” comes from Katsushika Hokusai, a famous Japanese artist during the Edo period. Hokusai was born in Katsushika-gun and present Edogawa-ku was also a part of Katsushika-gun in the era of Katsushika Hokusai.

Like Hokusai, edoxaban has emanated from Japan to the rest of the world.

What is Thrombosis?

Thrombosis is a condition in which a blood clot (thrombus) is formed within a blood vessel and blocks blood flow. Thrombosis is classified into arterial thrombosis and venous thrombosis.

Arterial thrombosis is a blood clot that is initiated by platelet aggregation within an artery (where blood flow is rapid) and may cause various diseases such as acute myocardial infarction. Prasugrel inhibits the formation of this type of thrombosis.

Venous thrombosis is a blood clot formed within a vein (where blood flow is slow). Blood coagulation may lead to the formation of a fibrin clot and cause cardioembolic stroke and venous thrombosis including economy-class syndrome. Edoxaban inhibits the formation of this type of thrombosis.

In 2013, Marketing applications for edoxaban in Japan, Europe, and the United States were submitted for the indications of the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for the treatment and secondary prevention of venous thromboembolism in patients with deep vein thrombosis or pulmonary embolism.

In developed countries, atrial fibrillation affects 1% to 2% of people, and venous thromboembolism causes the deaths of more than 500,000 patients in Europe and 300,000 patients in the United States every year.

With two different types of drugs for the treatment of various types of thrombosis, prasugrel and edoxaban, Daiichi Sankyo will continue to provide effective therapies for patients suffering from these conditions.
The Long Road of Research to Discovery of Edoxaban

Research and Development began exploring the development of a drug that might overcome some of the disadvantages of previously mentioned warfarin and that 1) is orally administered, 2) shows less individual variations, 3) is effective, 4) causes less major bleeding, and 5) does not require routine blood monitoring.

**Initiation of a program for FXa inhibitors**
An exploratory research project of FXa (activated coagulation factor X) inhibitors was started in 1979.

**Selection of three candidate compounds**
After more than 10 years of research and development, three candidate compounds were identified.

**World’s first discovery of a direct FXa inhibitor, DX-9065a**
The world’s first direct FXa inhibitor, DX-9065a, was discovered after 10 years of exploratory research. It was developed as an injection due to low oral absorption, and its efficacy and safety were studied in a clinical trial.

**Arterial thrombus formed in places where blood flow is fast.**
Platelet thrombus (white thrombus)
Prasugrel, an antiplatelet agent

**Venous thrombus formed in places where blood flow is slow.**
Fibrin thrombus (red thrombus)
Edoxaban, an anticoagulant
Phase 1 Clinical Trial to Global Clinical Trial of Edoxaban

A clinical trial was started by narrowing down many compounds to three candidate compounds. It took 10 years from 2003, when a phase 1 clinical trial was started, to 2013, when two global clinical trials, the Hokusai-VTE and ENGAGE AF-TIMI 48 trials, were completed.

Voice

With a lot of opportunities and challenges from edoxaban

My role (clinical pharmacology) is to select optimal doses in terms of risk-benefit balance. We evaluated the most suitable doses and incorporate them in the clinical study plans. After completing the studies, we analyzed the data and incorporated the results in the description of package insert. While I had worked on several projects and approval applications, this is the first time I was involved in a global study or a global simultaneous application prior to edoxaban. We experienced many difficulties in discussions with project team members from many functions within Daiichi Sankyo Group, and it was not always easy to reach the agreement in some of the meetings. I encountered a number of problems when I worked in the global team, including barriers of language, time and location. However, we achieved many things with the help of colleagues, and with science as our common language. Over a period of about ten years, as the project moved through Phase 1, Phase 2 and Phase 3, my roles expanded dramatically. Edoxaban provided me with both opportunities and challenges, through which I have learned a great deal. This time, I am here as only to follow a path laid out for me by colleagues. Next time, I should be ready and willing to start blazing a trail for others. It has inspired me to want to take on a new challenge and further to improve my abilities over the next ten years, so that I can contribute, in my own small way, to provide patients everywhere with drugs that address unmet medical needs to help patients with serious diseases.

Takako Shimizu Ph.D.

Clinical Pharmacology Group, Translational Medicine Department,
Japan Development Supervising Department, Research and Development Head Office
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**ENGAGE AF-TIMI 48 Trial**

This global study was conducted in 46 countries and compared the efficacy and safety of edoxaban 60 mg and 30 mg to those of warfarin in 21,105 patients with non-valvular atrial fibrillation.

The annual incidence of stroke or systemic embolic events, the primary efficacy endpoint, was 1.18% in the edoxaban 60 mg group, 1.61% in the edoxaban 30 mg group, and 1.50% in the warfarin group, demonstrating the non-inferiority of edoxaban 60 mg and 30 mg to warfarin.

The annual incidence of major bleeding, the primary safety endpoint, was 2.75% in the edoxaban 60 mg group, 1.61% in the edoxaban 30 mg group, and 3.43% in the warfarin group. Edoxaban 60 mg and 30 mg reduced the risk of major bleeding by 20% and 53%, respectively, compared to warfarin, demonstrating its superiority at both doses.

**Hokusai-VTE Trial**

This global study was conducted in 37 countries and compared the efficacy and safety of edoxaban to those of warfarin in 8,292 patients with symptomatic deep vein thrombosis or and pulmonary embolism.

The incidence of venous thromboembolism (VTE), the primary efficacy endpoint, was 3.2% in the edoxaban 60 mg group and 3.5% in the warfarin group, demonstrating the non-inferiority of edoxaban 60 mg and 30 mg to warfarin.

The incidence of major or clinically relevant non-major bleeding, the primary safety endpoint, was 8.5% in the edoxaban group and 10.3% in the warfarin group. Edoxaban reduced the risk of bleeding by 19%, compared to warfarin, demonstrating its superiority for the primary safety endpoint.
Edoxaban: Competitive Advantage

1. Unique combination of both once-daily convenience and less major bleeding than warfarin
Edoxaban currently approved for marketing only in Japan is administered once daily to patients with any of the indicated diseases, thus providing a high level of convenience.

2. Patient specific dosing based on patient’s condition
Unlike warfarin, edoxaban does not require to the patient to undergo periodic laboratory tests to monitor blood levels. Moreover, it has a flexible dosage regimen, allowing an optimal dose to be selected for patients at higher risk of bleeding.

3. Results from the large single comparative studies in SPAF and VTE with very high quality
The efficacy and safety profile of edoxaban has been confirmed based on data from two robust global phase 3 clinical trials.

4. Accumulated safety data from more than 150,000 patients in Japan
In Japan, edoxaban was launched in July 2011 as a drug for the prevention of venous thromboembolism after major orthopedic leg surgeries. For approximately three years since its market launch, edoxaban has been administered in more than 150,000 patients. Therefore, a substantial body of safety data had been accumulated by the time supplemental new drug application for AF and VTE indications was submitted.

In two large-scale global clinical trials, ENGAGE AF-TIMI 48 and Hokusai-VTE, the non-inferiority of the efficacy of edoxaban and superiority of its safety in the incidence of clinically significant bleeding were evidenced against warfarin in 2013. The drug was submitted for marketing approval in Japan, the United States, and Europe for the reduction in risk of stroke and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation (NVAF) based on the results of the ENGAGE AF-TIMI 48 study and for the treatment and recurrence prevention of venous thromboembolism (VTE) based on the Hokusai-VTE study.

Voices

Thanks to my fate as a person responsible for the global clinical trials of edoxaban

Edoxaban is part of my life. It was exciting to join Daiichi Sankyo to work in thrombosis again since my days at the University of Perugia. Truthfully, I could not predict how intense my days were going to be. I couldn’t predict what would have been necessary to do to get the job done. But this is, essentially, why I am so fortunate, having a fantastic job filled with science, medicine, methodology, innovation, and excellence. All are necessary to fulfill a single goal; offering new therapies to patients and their doctors. 2013 was the pinnacle of my scientific career. It was rewarding to work with many talented colleagues. It was humbling to work closely with the best academic minds and learn almost daily from Dr. Eugene Braunwald and Professor Harry Buller. It was electrifying to listen to the presentations of Hokusai VTE and ENGAGE AF-TIMI 48 at the European Society of Cardiology (Amsterdam) and at the American Heart Association (Dallas). I was left speechless to see the articles in the prestigious New England Journal of Medicine. Grazie edoxaban.

Michele Mercuri, MD, Ph.D.
Senior Vice President
Chief Medical Advisor and North America Head of Clinical Development
Daiichi Sankyo Pharma Development
Future of Edoxaban

Daichi Sankyo Group has accumulated variety of experiences in the fields of cardiovascular and thrombosis through olmesartan (launched in Europe and in the United States in 2002) and with prasugrel (launched in 2009). In Europe and USA, Daichi Sankyo has achieved great success by marketing this product almost on our own with olmesartan, and also has developed strong relationships with thrombosis specialists through the co-promotion business with prasugrel. In addition, we have the top-class commercial capabilities in Japan in terms of both “quality” and “quantity” as shown through the increase of sales recently.

We have considered various options to optimize the global launch and marketing strategies for edoxaban. During this exercise, we have concluded that the capabilities necessary in the anticoagulant market requires more of “quality” rather than “quantity”. For example, the required “quality” includes capabilities to adequately respond to the needs of specialists who make the initial treatment decisions, and also other key stakeholders such as other health care providers, payers and patient organizations. We have considered that these capability “quality” would become more important than having capability “quantity” that is represented by putting more weight on providing traditional share of voice through the sales reps.

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**Engage AF TIMI 48**

The treatment and prevention of the recurrence of venous thromboembolism (VTE) in patients with DVT(1) /PE(2)

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**Hokusai VTE**

(1) DVT: Deep vein thrombosis, (2) PE: Pulmonary embolism

ASCA: Asia, South and Central America