Press Release

FDA Approves XOFLUZA™ (Baloxavir Marboxil) for the Treatment of Acute Uncomplicated Influenza for People at High Risk of Developing Influenza-Related Complications

OSAKA, Japan, October 18, 2019 - Shionogi & Co., Ltd. (hereafter "Shionogi") has announced that the United States (U.S.) Food and Drug Administration (FDA) has approved Roche Group's supplemental New Drug Application (sNDA) for XOFLUZA™ (baloxavir marboxil) for the treatment of acute, uncomplicated influenza in people 12 years of age and older who have been symptomatic for no more than 48 hours and who are at high risk of developing influenza-related complications. The sNDA was based on the global phase III study, CAPSTONE-2. The approval came earlier than November 4, 2019, the Prescription Drug User Fee Act (PDUFA) date for an FDA decision.[1]

The Centers for Disease Control and Prevention (CDC) recommends antiviral treatment as early as possible for patients at high risk for influenza-related complications.[2]
"Influenza can lead to serious health consequences such as hospitalization or even death especially in individuals who are at high risk of developing complications from influenza." said Dr. Tsutae "Den" Nagata, Chief Medical Officer at Shionogi. "There are no other antiviral medicines indicated specifically for the treatment of influenza in high-risk populations. Therefore, we believe that XOFLUZA will be an important treatment option for individuals at high risk for influenza complications in the U.S."

Shionogi and Roche Group (hereafter "Roche") are in a license and collaboration agreement to develop and commercialize XOFLUZA. Under the terms of this agreement, Roche holds worldwide rights to XOFLUZA excluding Japan and Taiwan where the rights are retained exclusively by Shionogi. XOFLUZA was first approved by the FDA for the treatment of acute, uncomplicated influenza in otherwise healthy people 12 years of age and older who have been symptomatic for no more than 48 hours on October 25, 2018.[3]

Shionogi's research and development efforts target infectious diseases as one of its priority areas, and Shionogi has defined "protecting people from the threat of infectious diseases" as one of its core social missions. Shionogi strives constantly to bring forth innovative drugs for the treatment of infectious diseases, to protect the health of the many patients we serve. Shionogi will continue to work diligently to collect and analyze data on the efficacy and safety of XOFLUZA and provide information for appropriate use.

About XOFLUZA

XOFLUZA, discovered by Shionogi, has a novel mechanism of action that inhibits cap-dependent endonuclease in the polymerase acidic (PA) protein (in the United States Prescribing Information, this enzyme is stated as polymerase acidic endonuclease), an enzyme essential for viral replication. The regimen for XOFLUZA is a single-oral dose to treat uncomplicated influenza, which is different from all currently available antiviral treatments. In non-clinical studies, XOFLUZA demonstrated an antiviral effect against a wide range of influenza viruses including oseltamivir-resistant strains and avian strains (H7N9, H5N1).[4, 5] XOFLUZA is currently approved in several countries including Japan and the U.S. XOFLUZA was approved and is now available in Japan for the treatment of influenza types A and B in adults and pediatric patients.[6] In addition, XOFLUZA was approved in Taiwan on August 28, 2019, for the treatment of acute influenza Types A and B in patients aged 12 years of age and older.[7] For more information about the use in the U.S., please refer to the XOFLUZA website.

Roche is now conducting a phase III development program including children under the age of one year, and severely ill, hospitalized patients, as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people. Shionogi is assessing the potential of XOFLUZA as a post-exposure prophylaxis treatment to prevent the spread of influenza in adults and children, and positive results were obtained in the Phase III study.[8]

About the CAPSTONE-2 Study[9]

The CAPSTONE-2 study was a phase III, multicenter, randomized, double-blind study that evaluated a single oral dose of XOFLUZA compared with placebo and oseltamivir in patients 12 years of age or older who are at a high risk for influenza-related complications. The study was conducted globally by Shionogi. A total of 2184 participants enrolled in the study were randomly assigned to a single dose of 40 mg or 80 mg of baloxavir marboxil (according to body weight), placebo or 75 mg of oseltamivir twice a day for 5 days. Among them, 1163 (53%) patients were confirmed to have influenza virus infection with RT-PCR (influenza virus subtype: 47.9% for A/H3N2, 6.9% for A/H1N1, 41.6% for B). The most common risk factors were asthma or chronic lung disease (39.2%), age ≥65 years (27.4%), endocrine disorders (32.8%), metabolic disorders (13.5%), heart disease (12.7%), and morbid obesity (10.6%). The study was conducted globally by Shionogi. Key results from CAPSTONE-2 are as follows:

- XOFLUZA significantly reduced the time to improvement of influenza symptoms versus placebo in people at high risk of complications from influenza (median time 73 hours versus 102 hours; $p<0.001$).
- In subjects infected with type B virus, the median time to improvement of influenza symptoms was significantly shorter in the XOFLUZA group compared to the placebo group (75 hours versus 101 hours respectively).
- Adverse events reported in at least 1% of adult and adolescent subjects treated with XOFLUZA included diarrhoea (3%), bronchitis (3%), nausea (2%), sinusitis (2%) and headache (1%). XOFLUZA was well-tolerated and no new safety signals were identified.

About Influenza

Seasonal and pandemic influenza remain a major public health concern, and novel influenza drugs that offer significant improvement over current therapy are urgently needed. Globally, seasonal epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths every year.[10, 11, 12, 13, 14] The CDC describes high-risk categories as including children under 2 years of age, adults of 65 years of age and older, pregnant women, and people of any age with certain medical conditions, including asthma and chronic lung disease, heart disease, blood disorders, endocrine disorders, metabolic diseases, extreme obesity and weakened immune systems.[2]

About Shionogi

Shionogi & Co., Ltd. is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company currently markets products in several therapeutic areas including anti-infectives, pain, cardiovascular diseases and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more information on Shionogi & Co., Ltd., visit www.shionogi.co.jp/en.

Forward-Looking Statements

This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

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References

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FDA Accepts XOFLUZA™ (Baloxavir Marboxil) Supplemental New Drug Application for the Treatment of Influenza in Individuals at High Risk for Influenza-Related Complications

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Shionogi Announces FDA Approval of XOFLUZA™ (Baloxavir Marboxil) for the Treatment of Acute, Uncomplicated Influenza
4. T. Noshi et al. In vitro Characterization of Baloxavir Acid, a First-in-Class Cap-dependent Endonuclease Inhibitor of the Influenza Virus Polymerase PA Subunit. Antiviral Research 2018;160:109-117
5. K. Taniguchi et al. Inhibition of avian-origin influenza A(H7N9) virus by the novel cap-dependent endonuclease inhibitor baloxavir marboxil. Scientific Reports volume 9, Article number: 3466 (2019)
6. Press release on March 14, 2018
XOFLUZA™ (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
7. Press release on August 29, 2019
Shionogi Announces XOFLUZA® Tablets 20mg for The Treatment of Influenza Types A and B in Patients 12 years of Age and older Approved in Taiwan
8. Press release on September 2, 2019
Shionogi Announces Positive Post-Exposure Prophylaxis Results for XOFLUZA® in Phase III Study (BLOCKSTONE) of Influenza Virus Infection in Household Members
9. Press release on October 4, 2018
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