Press Release

Shionogi Announces XOFLUZA® Tablets 20mg for the Treatment of Influenza A or B virus Acute Infection Launched in Taiwan.

OSAKA, Japan, November 25, 2019 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that Xofluza® launched in Taiwan for the treatment of influenza A or B virus acute infection in patients adults and children 12 years of age and older.

Xofluza®, discovered by Shionogi, inhibits cap-dependent endonuclease, an essential enzyme for viral replication. Xofluza® was approved in Taiwan on August 28, 2019.[1] Taiwan Shionogi & Co., Ltd., (hereafter “Taiwan Shionogi”), the Taiwan subsidiary of Shionogi, is responsible for selling Xofluza® in Taiwan.

Shionogi and Roche Group (hereafter “Roche”) are in a license and collaboration agreement to further 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® is approved and is available in Japan.[2] In the U.S., Xofluza® is available for the treatment of acute, uncomplicated influenza in people 12 years of age or older who have been symptomatic for no more than 48 hours[3] and is recommended for the treatment of acute, uncomplicated influenza in people 12 years of age or older in the guidelines of the Centers for Disease Control and Prevention (CDC).[4] In addition, Roche’s supplemental New Drug Application (sNDA) of Xofluza® for the treatment of acute, uncomplicated influenza in people aged 12 years and older, who have been symptomatic for no more than 48 hours and who are at high risk of influenza-related complications, was approved by the U.S. Food and Drug Administration (FDA) on October 16, 2019.[5] This was based on the efficacy and safety results of a global phase III study (CAPSTONE-2).[6]

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 other 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).[7, 8] Xofluza, has been reviewed and is currently approved in several countries including Japan and the U.S. 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(NCT03653364), and severely ill, hospitalized patients(NCT03684044), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people(NCT03969212).

Shionogi assessed 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 BLOCKSTONE study.[9]

About CAPSTONE-1 Study

The CAPSTONE-1 study was a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study that enrolled 1,436 otherwise healthy patients 12 years of age and older diagnosed with influenza. In this study, XOFLUZA significantly reduced the time to alleviation of symptoms compared with placebo (median time; 53.7 hours versus 80.2 hours; $p<0.0001$) and demonstrated clinical efficacy which was not significantly different from that of oseltamivir (median time; 53.5 hours versus 53.8 hours). XOFLUZA was generally well tolerated with a numerically lower overall incidence of adverse events reported compared with both placebo and oseltamivir (incidence of adverse events; 20.7% for XOFLUZA, 24.6% for placebo, 24.8% for oseltamivir).
The CAPSTONE-1 and Phase II study results were published in the September 6, 2018 issue of the New England Journal of Medicine.[10]

About the CAPSTONE-2 Study[6]

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 Taiwan Shionogi & Co., Ltd

Taiwan Shionogi & Co., Ltd was incorporated locally in Taiwan in 1963. It is a wholly owned subsidiary, and also the oldest subsidiary of Shionogi & Co., Ltd, headquartered in Osaka, Japan. Taiwan Shionogi has long history of developing drugs especially in the field of antibiotics and anti-infective agents to save the lives and wellbeing of patients. Under the corporate mission, Taiwan Shionogi continuously strives to save the lives of patients and improving their quality of life by providing better medicines. In addition to the sales expansion of its main existing antibiotic Flumarin®

and Finibax®, and anti flu drug Rapiacta®, Taiwan Shionogi is making its best efforts to introduce new drugs and aiming at contributing to the medium-and-long term growth of the Shionogi Group.

About Influenza

Seasonal, epidemic and pandemic influenza remain a major public health concern, and novel influenza drugs that will offer significant improvement over current therapy are urgently needed. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths worldwide.[11, 12, 13, 14, 15] In general, those at highest risk of influenza-related complications include children under 2 years of age, adults over 65 years of age, pregnant women, and people of any age with certain medical conditions, including chronic heart, lung, metabolic diseases (such as diabetes) and weakened immune systems.[16]

In Taiwan, approximately 14% of the population need treatments for influenza or related pneumonia every year.[17] The influenza epidemic period occurs in the winter, from late November through March. The overall health impact (e.g., infections, hospitalizations, and deaths) of a flu season varies from year to year. Taiwan CDC monitors circulating flu viruses and their related disease activity and provides influenza reports (Influenza Express) each week from October through May. In Taiwan, among outpatient cases of influenza, about 0.5% require hospitalization, of which 7% of the patients with serious complications need intensive care, and of which the mortality rate is about 20%.[18]

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.

For Further Information, Contact:

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References

1. 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
2. Press release on March 14, 2018

XOFLUZA (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
3. Press release on October 25, 2018
Shionogi Announces FDA Approval of XOFLUZATM (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza –
4. CDC Guideline
CDC website, Influenza Antiviral Medications: Summary for Clinicians.
5. Press release on October 18, 2019
FDA Approves XOFLUZA™ (Baloxavir Marboxil) for the Treatment of Acute Uncomplicated Influenza for People at High Risk of Developing Influenza-Related Complications
6. Press release on October 4, 2018
Shionogi Presents Positive Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications at IDWeek 2018
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9. 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
10. Press release on September 6, 2018
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