Press Release

Shionogi Provides Update on the Japanese Association for Infectious Diseases Statement and the Revised Guidelines of the Japanese Pediatric Society for the Treatment of Influenza

OSAKA, Japan, October 28, 2019 – Shionogi & Co., Ltd (Head Office: Chuo-ku, Osaka; President & CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") would like to share an update on the announcements made by two healthcare professionals' (HCPs) associations; the Japanese Association for Infectious Diseases (JAID) and the Japanese Pediatric Society (JPS). The JAID statement for the treatment of influenza (flu) and the JPS guidelines for the treatment of flu for the 2019–2020 season were disclosed on their websites, respectively. The JAID and JPS provide considerations for HCPs on the overall management of flu patients, and the use of vaccines and anti-influenza medicines, including XOFLUZA® (baloxavir marboxil), a Shionogi antiviral medicine for the treatment of flu, among other topics.

The JAID Statement

The JAID statement suggests the use of XOFLUZA as follows:

1) ≥12 to 19 years of age and adults: No decision on a recommendation for XOFLUZA use has been made at present due to limited clinical data.
2) Children <12 years of age: Careful consideration of the use of XOFLUZA, taking into account the high rates of emergence of variant viruses with reduced susceptibility to XOFLUZA in children observed in clinical studies to date.
3) Immunocompromised and severe influenza patients: No recommendation on active use of XOFLUZA as monotherapy.*

These considerations aim to support informed clinical decision making based on currently available information, mainly data published in scientific journals; however, HCPs have discretion in their interpretation of the statement based on individual patient needs. Upon careful analysis of the available clinical data for XOFLUZA, JAID has decided not to provide a definitive recommendation for XOFLUZA use at present, but has confirmed multiple seasons of data are normally required before a recommendation for XOFLUZA can be issued.

The JPS Guidelines

The JPS guidelines are generally revised every year ahead of the upcoming flu season based on currently available information, mainly data published in scientific journals. The guidelines suggest the use of XOFLUZA in pediatric patients as follows:

1) The committee does not actively recommend the use of XOFLUZA in pediatric patients <12 years of age, as the reports of the clinical experience of XOFLUZA in this population are currently limited and the emergence of resistant viruses has been observed.
2) While the use of XOFLUZA is not to be restricted for the time being, the emergence and potential transmission of resistant viruses needs to be carefully monitored.
3) For the treatment of immunocompromised patients, XOFLUZA should not be used as monotherapy as the shedding of resistant viruses may be prolonged. In the case of severe influenza or influenza complicated with pneumonia, combination therapy with XOFLUZA and other anti-flu drug(s) could be considered, although the committee views that the current level of clinical evidence is insufficient and are in the process of collecting and assessing such data.*

*Please note the potential usage of XOFLUZA in this patient population(s) is not approved by the PMDA

The JPS developed their guidelines for XOFLUZA use in pediatric patients with consideration of the following; limited reports of the clinical experience and the potential emergence of variant viruses with reduced susceptibility to XOFLUZA (JPS expresses as “resistant viruses”). These considerations are common to key topics discussed by the JAID.

XOFLUZA is the first drug to demonstrate clinical benefits in both otherwise-healthy and high-risk flu patients in randomized clinical studies.[1, 2] In a study of high-risk flu patients, XOFLUZA significantly reduced the time to improvement of influenza symptoms in influenza type B compared with oseltamivir and the incidence of influenza-related complications compared with placebo.[3] In the U.S., XOFLUZA 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] The U.S. Food and Drug Administration (FDA) also recently approved the Roche Group’s supplemental New Drug Application (sNDA) for XOFLUZA for the treatment of acute, uncomplicated influenza in people aged 12 years and older, and are at high risk of developing influenza-related complications.[5] Furthermore, a global pediatric study demonstrated that XOFLUZA was a well-tolerated and effective potential treatment for flu in otherwise healthy children aged one to less than 12 years old.[6]

Shionogi has published data on the occurrence of treatment-emergent PA/I38X-substituted viruses from drug surveillance conducted in the 2018–2019 season and additional analyses of completed clinical studies.[7, 8] In clinical trials to date, analyses show that in the overall study populations, treatment with XOFLUZA remains well-tolerated and demonstrated clinical benefit even if variant viruses with reduced susceptibility to XOFLUZA emerged. Although some of these studies have been published as original papers, [9, 10] the results of other studies including the studies on high-risk flu patients and pediatrics have not been cited in JAID statement and JPS guidelines because they are currently being submitted to peer-reviewed journals. Shionogi will make efforts to publish in primary scientific journals as soon as possible.

It is known that the type/subtype of influenza virus varies by season, as well as the rates of variant viruses with resistance to anti-influenza drugs. As with all antiviral medicines, treatment-emergent variant viruses with reduced-susceptibility have been seen in patients taking XOFLUZA (most commonly PA/I38X-substituted viruses). It is therefore important to continue to collect data about the incidence rate and to further investigate potential effects on clinical symptoms of PA/I38X-substituted viruses throughout several upcoming seasons. Shionogi will continue to proactively monitor and characterize PA/I38X-substituted viruses by cooperating with various surveillance programs in Japan, as well as conducting global surveillance with the Roche Group, and will communicate findings to medical institutions and guideline committees, including JAID and JPS, and at academic conferences as quickly as possible when data becomes available. We will also continue fulfilling our social responsibilities as a company manufacturing innovative medicines for infectious diseases.

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 proper use.

About XOFLUZA (baloxavir marboxil)
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).[11, 12]

XOFLUZA is currently approved in several countries including Japan and the U.S.[13, 14] In addition, XOFLUZA was approved in Taiwan on August 28, 2019, for the treatment of acute influenza types A and B in patients 12 years of age and older.[15] On October 16, 2019, the U.S. FDA approved a supplemental New Drug Application for XOFLUZA for the treatment of acute, uncomplicated influenza in people aged 12 years and older, and are at high risk of developing influenza-related complications.[5] For more information, please refer to the XOFLUZA website.

Shionogi and the Roche Group, which includes Genentech in the U.S., have a license and collaboration agreement to further develop and commercialize XOFLUZA globally. Under the terms of this agreement, the Roche Group holds worldwide rights to XOFLUZA excluding Japan and Taiwan, which will be retained exclusively by Shionogi & Co., Ltd.

Roche Group is now conducting a phase III development program including in a pediatric population under one year, hospitalized patients with severe influenza and will assess the potential to reduce transmission of influenza from an infected person to healthy people.

About Influenza
Seasonal and pandemic influenza remain a major public health concern, and novel influenza drugs that will offer significant improvements over current therapies 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. [16, 17, 18, 19, 20] The Centers for Disease Control and Prevention (CDC) defines people at high-risk of serious flu complications as those who have conditions such as asthma, chronic lung disease, diabetes, heart disease or morbid obesity, or adults 65 years of age or older.[21]

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 outcomes 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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   Shionogi Announces Positive Top-Line Results for S-033188 Phase 3 Study (CAPSTONE-1) in Otherwise Healthy Influenza Patients
2. Press release on July 17, 2018
   Shionogi Announces Positive Top-Line Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications
3. 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
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 September 2, 2019
   Positive Results for XOFLUZA™ Global Phase III Study (MINISTONE-2) in Children with Influenza
7. Press release on September 2, 2019
   The Results of Analyses of PA/I38X-substituted Viruses in XOFLUZA® Clinical Studies
8. Press release on September 2, 2019
   Special Drug Use Survey for XOFLUZA® Announced at OPTIONS X - Analysis of Rate of

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XOFLUZA™ (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
14. Press release on October 25, 2018
Shionogi Announces FDA Approval of XOFLUZA™ (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza
15. 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
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