Press Release

Shionogi Announces Supplemental New Drug Application for XOFLUZA® in Japan for the Post-Exposure Prophylaxis of Influenza Virus Infection was Approved.

OSAKA, Japan, November, 27, 2020 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that Shionogi received approval for the supplemental New Drug Application (sNDA) for XOFLUZA® for the post-exposure prophylaxis of influenza virus infection. The sNDA is based on data from the phase III BLOCKSTONE study.[1, 2]

Vaccination is widely available for the prevention of influenza virus infection, but since the type of influenza virus that prevails varies depending on the season, vaccination alone is not enough to completely control viral infections, onset, and exacerbation. Therefore, prophylactic administration of anti-influenza virus drugs has become an important option for preventing influenza in high-risk patients including chronic lung disease, metabolic disorders, age ≥65 years,[3] within family with confirmed ifluenza. In particular, in hospitals and facilities for the elderly, in addition to robust vaccination and infection prevention measures, it is recommended by JAID to proactively administer anti-influenza virus drugs to healthy individuals exposed to someone with influenza from an early stage.[4]

We are aware of and understand the concerns about the influenza season coinciding with theCOVID-19 pandemic this year. In addition to infection prevention measures such as droplet infection precautions and hand hygiene, vaccination is strongly recommended for the prevention of influenza virus infections, and the importance of preventing influenza is increasing.[5] With this approval, single-dose Xofluza® has become a new option for the prevention of influenza post-exposure, and is expected to contribute not only for the treatment of influenza (as per its existing approval) but also now for prevention upon exposure.

Shionogi is committed to “Protect people worldwide from the threat of infectious diseases” as our key focus. We are not limiting ourselves to the research and development of therapeutic medications, but are also focused on the total care of infectious disease through awareness building, prevention and diagnosis and suppression of exacerbation. Shionogi will continue to work diligently to collect and analyze data on the efficacy and safety of Xofluza® and provide information for appropriate use.

'XOFLUZA®' Product Description

<table>
<tr><td>Product Name</td><td>XOFLUZA® Tablets 10mg/20mg/granule 2%</td></tr>
<tr><td>Indications</td><td>XOFLUZA® Tablets 20mg/granule 2%
Treatment and Prevention of Influenza Types A and B
XOFLUZA® Tablets 10mg
Treatment of Influenza Types A and B</td></tr>
<tr><td>Dosage and Administration:</td><td>The following doses are usually given orally in a single dose.

1. Treatment
Adults and children over 12 years
<table>
<tr><td>Body weight</td><td>Dosage</td></tr>
<tr><td>80kg or more</td><td>Four 20mg tablets or 8 packages granules
(80 mg as baloxavir marboxil)</td></tr>
<tr><td>Less than 80 kg</td><td>Two 20mg tablets or 4 packages granules
(40 mg as baloxavir marboxil)</td></tr>
</table>
Children under 12 years
<table>
<tr><td>Body weight</td><td>Dosage</td></tr>
<tr><td>40kg or more</td><td>Two 20mg tablets or 4 packages granules
(40 mg as baloxavir marboxil)</td></tr>
<tr><td>Less than 40 kg
and 20 kg or more</td><td>One 20mg tablet or 2 packages granules
(20 mg as baloxavir marboxil)</td></tr>
<tr><td>Less than 20kg
and 10kg or more</td><td>One 10mg tablet
(10 mg as baloxavir marboxil)</td></tr>
</table>

2. Prevention
Adults and children over 12 years
<table>
<tr><td>Body weight</td><td>Dosage</td></tr>
<tr><td>80kg or more</td><td>Four 20mg tablets or 8 packages granules
(80 mg as baloxavir marboxil)</td></tr>
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</td></tr>
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About the BLOCKSTONE Study[1]

BLOCKSTONE was a Phase III, double blind, multicenter, randomised, placebo-controlled, post-exposure prophylaxis study that evaluated a single-dose of Xofluza® compared with placebo in household members (adults and children) who were living with someone with an influenza infection confirmed by a rapid influenza diagnostic test (the 'index patient'). The study was conducted by Shionogi & Co., Ltd. during the 2018-2019 flu season in Japan.

Those diagnosed with influenza were required to have onset of symptoms within less than 48 hours, and participants were required to have lived with those diagnosed for more than 48 hours. The participants were randomised to receive a single-dose of Xofluza® (dosed according to body weight) or placebo as a preventive measure against developing influenza.

Xofluza® showed a statistically significant prophylactic effect on influenza after a single-dose in people exposed to an infected household contact. The proportion of household members 12 years of age and older who developed influenza was 1.9% in participants treated with Xofluza® and 13.6% in the placebo-treated group. Xofluza® was well tolerated in this study and no new safety signals were identified. The result of the BLOCKSTONE study, which was recently published in The New England Journal of Medicine. [1]

About Xofluza® (baloxavir marboxil)

Xofluza® discovered by Shionogi, has a novel mechanism of action that inhibits the 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. Xofluza® is a single-dose oral treatment for 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).[6, 7]

Shionogi and the 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 available many countries for the treatment of influenza types A and B, including Japan and the U.S.

In U.S., the FDA has approved for a sNDA for Xofluza® as a treatment to prevent influenza in people 12 years of age and older following contact with someone with influenza (known as post-exposure prophylaxis) on November 23, 2020.[8] On November 12th, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorization for XOFLUZA for the treatment of uncomplicated influenza in patients aged 12 years and above. In addition, the CHMP has also adopted a positive opinion for XOFLUZA for the preventive treatment (post-exposure prophylaxis) of influenza in individuals aged 12 years and above following contact with someone with influenza.[9]

Roche is conducting a phase III development program investigating Xofluza® in several populations, including children under the age of one year (NCT03653364), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people (NCT03969212). Shionogi filed sNDA for Xofluza® in Taiwan for the post-exposure prophylaxis of influenza virus infection in adults and children 12 years of age and older on March 31, 2020 based on the positive results from the Phase III BLOCKSTONE study.[10]

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. Hideyuki Ikematsu, MD et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. N Engl J Med 2020 Jul 8
https://www.nejm.org/doi/full/10.1056/NEJMoa1915341
2. Press release on October 16, 2019
Shionogi Filed for the Supplemental New Drug Application of XOFLUZA® in Japan for the Post-Exposure Prophylaxis of Influenza Virus Infection
3. CDC Criteria
CDC website, People at High Risk For Flu Complications
4. JAID statement 2012 “Concept of Influenza Hospital Infection Countermeasures” (Including Facilities for the Elderly)
http://www.kansensho.or.jp/modules/guidelines/index.php?content_id=24
5. JAID statement “Preparing for the simultaneous epiemics of influenza and COVID-19”
http://www.kansensho.or.jp/uploads/files/guidelines/2008_teigen_influenza_covid19.pdf
6. 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
7. 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)
8. Press release on November 24, 2020
Shionogi Announces FDA Approval of XOFLUZA® (Baloxavir Marboxil) for the prevention of Influenza following contact with an infected person.
9. Xofluza: Pending EC decision|European Medicines Agency
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/xofluza

10. Press release on March 31, 2020
    Shionogi Filed for the Supplemental New Drug Application of Xofluza® in Taiwan for the Post-Exposure Prophylaxis of Influenza Virus Infection