

Roche announces FDA approval of Xofluza (baloxavir marboxil) for influenza

- **First and only single-dose oral medicine approved to treat the flu**
- **Xofluza significantly reduced the duration of flu symptoms compared to placebo**
- **First novel proposed mechanism of action to treat the flu in nearly 20 years**

Basel, 24 October 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the US Food and Drug Administration (FDA) has approved Xofluza™ (baloxavir marboxil) for the treatment of acute, uncomplicated influenza, or flu, in people 12 years of age and older. Xofluza is a first-in-class, single-dose oral medicine with a novel proposed mechanism of action that inhibits polymerase acidic endonuclease, an enzyme essential for viral replication.^[1-2] Xofluza has demonstrated efficacy against a wide range of influenza viruses, including oseltamivir-resistant strains and avian strains (H7N9, H5N1) in non-clinical studies.^[3-5]

“Xofluza is the first new flu medicine with a novel proposed mechanism of action approved in nearly 20 years, and we’re excited to offer a convenient treatment option that reduces flu symptoms by more than a day with a single oral dose,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “If patients see their doctors within 48 hours of symptom onset, one dose of Xofluza can significantly reduce the duration of flu symptoms.”

The flu is one of the most common, yet serious, infectious diseases, representing a significant threat to public health. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalisations and up to 650,000 deaths worldwide.^[6-9]

Xofluza was approved based on results from the phase III CAPSTONE-1 study of a single-dose of Xofluza compared with placebo or oseltamivir 75 mg, twice daily for five days, in otherwise healthy people with the flu, as well as results from a placebo-controlled phase II study in otherwise healthy people with the flu. Xofluza significantly reduced the duration of flu symptoms compared to placebo, and demonstrated similar efficacy compared to oseltamivir.^[10] In clinical trials, Xofluza was safe and well-tolerated with a side effect profile similar to placebo. The CAPSTONE-1 and phase II study results were recently published in the 6 September 2018 issue of the [New England Journal of Medicine](#).^[10]

About CAPSTONE-1^[10]

CAPSTONE-1 was a phase III multicentre, randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of Xofluza in 1,436 people age 12 and older in the US and Japan. The primary endpoint of the study was time to alleviation of symptoms. The study found the following results:

- Xofluza met its primary endpoint compared to placebo:
 - Significantly reduced the duration of flu symptoms by more than one day (median time 54 hours versus 80 hours; $p < 0.001$);
- Similar efficacy results were seen between Xofluza and oseltamivir in relation to duration of symptoms (median time 54 hours versus 54 hours).

The most common adverse events reported were diarrhoea (3.0%), bronchitis (2.6%), nausea (1.3%) and sinusitis (1.1%), and all of these adverse events occurred at a lower frequency than placebo. The study was conducted in the US and Japan by Shionogi & Co., Ltd.

About Xofluza™ (baloxavir marboxil)

Xofluza is a first-in-class, single-dose oral medicine with a novel proposed mechanism of action that demonstrated efficacy in a wide range of influenza viruses, including oseltamivir-resistant strains and avian strains (e.g. H7N9, H5N1) in non-clinical trials.^[3-5] Unlike other currently available antiviral treatments, Xofluza is the first in a new class of antivirals designed to inhibit polymerase acidic endonuclease, an enzyme essential for viral replication.^[1,2]

Roche recently announced that the global phase III CAPSTONE-2 study assessing the safety and efficacy of Xofluza in people at high risk of complications from the flu, as defined by the Centers for Disease Control and Prevention (CDC), met the study's primary objective and showed superior efficacy in the primary endpoint of time to improvement of influenza symptoms versus placebo.^[11] Xofluza will also be further studied in a phase III development programme including paediatric populations, post-exposure prophylaxis and severely ill hospitalised people with influenza, as well as to assess the potential to reduce transmission in otherwise healthy people.

Xofluza was discovered by Shionogi & Co., Ltd. and is being further developed and commercialised globally in collaboration with the Roche Group (which includes Genentech in the US). Under the terms of this agreement, Roche holds worldwide rights to Xofluza excluding Japan and Taiwan, which will be retained exclusively by Shionogi & Co., Ltd. Xofluza was approved in February 2018 by the Japanese Ministry of Health, Labour and Welfare for the treatment of influenza types A and B in adult and paediatric patients, and is being commercialised in Japan and marketed under the brand name Xofluza®

About Roche in influenza

Influenza, or flu, is one of the most common, yet serious, infectious diseases, representing a significant threat to public health. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalisations and up to 650,000 deaths worldwide.^[6-9] Roche has a long heritage in developing medicines that contribute to public health. We are committed to bringing innovation in the field of infectious diseases, including influenza. Tamiflu™ (oseltamivir) has made a significant difference both to the treatment of seasonal influenza as well as in the management of recent pandemics, and we are proud to have brought this innovative medicine to patients. Although vaccines are an important first line of defence in preventing the flu, there is a need for new medical options for prophylaxis and treatment. Current antiviral drugs have limitations with respect to efficacy, convenience of dosing, and resistance. Roche is committed to addressing the unmet need in this area through its agreement with Shionogi & Co., Ltd. to develop and commercialise Xofluza.

About Roche in infectious disease

Infectious diseases caused by viral or bacterial pathogens are a major cause of death and morbidity worldwide, and constitute an ever-growing medical need. As such, they form a core area of research and

development at Roche, with clinical development programmes focused on Hepatitis B, influenza and multi-drug resistant bacterial infections. We are committed to developing medicines that aim to be transformative, personalised, and accessible.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the tenth consecutive year, Roche has been recognised as the most sustainable company in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2017 employed about 94,000 people worldwide. In 2017, Roche invested CHF 10.4 billion in R&D and posted sales of CHF 53.3 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

All trademarks used or mentioned in this release are protected by law.

References

- [1] Shi F, et al. Viral RNA polymerase: a promising antiviral target for influenza A virus. *Curr Med Chem*. 2013;20(31):3923–34.
- [2] Kawaguchi K, et al. Effects of S-033188, a cap-dependent endonuclease inhibitor, on influenza symptoms and viral titer: Results from a phase 2, randomized, double-blind, placebo-controlled study in otherwise healthy adults with seasonal influenza. Poster presented at ESWI 2017.
- [3] T. Noshi et al. S-033447/S-033188, a Novel Small Molecule Inhibitor of Cap-dependent Endonuclease of Influenza A and B Virus: In Vitro Antiviral Activity against Laboratory Strains of Influenza A and B Virus in Madin-Darby Canine Kidney Cells. Poster presentation at OPTIONS IX, August 2016.
- [4] Taniguchi K, et al. Inhibitory Effect of S-033188, a novel inhibitor of influenza virus cap-dependent endonuclease, against avian influenza A/H7N9 virus in vitro and in vivo. Poster presentation at ESWI, September 2017.
- [5] Taniguchi K, et al. Inhibitory Effect of S-033188/S-033447, a novel inhibitor of influenza virus cap-dependent endonuclease, against highly pathogenic avian influenza virus A/H5N1. Poster presentation at ECCMID, April 2017.
- [6] World Health Organization. Influenza (Seasonal) [Internet; cited 2018 Oct]. Available from: <http://www.who.int/mediacentre/factsheets/fs211/en>.
- [7] Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. *Hum Vaccin Immunother*. 2016; 12(10):2712-2717.
- [8] Centers for Disease Control and Prevention. Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States. [Internet; cited 2018 Oct]. Available from: <https://www.cdc.gov/flu/about/disease/2015-16.htm>.

[9] Nair H, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011 Dec 3;378(9807):1917-30.

[10] Hayden F, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med 2018; 379:913-923.

[11] Ison M, et al. CAPSTONE-2 trial. Infectious Disease Week; 2018 Oct 3-7; San Francisco. CA, USA. Abstract #LB16. Available from: <https://idsa.confex.com/idsa/2018/webprogram/Paper74204.html>.

Roche Group Media Relations

Phone: +41 61 688 8888 / e-mail: media.relations@roche.com

- Nicolas Dunant (Head)

- Patrick Barth

- Ulrike Engels-Lange

- Simone Oeschger

- Anja von Treskow