FDA accepts Roche's supplemental new drug application for Xofluza™ (baloxavir marboxil) for the treatment of influenza in people at high risk of complications

- **Xofluza would be the first antiviral medicine approved specifically for the high-risk population**

Basel, 6 March 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the United States (U.S.) Food and Drug Administration (FDA) has accepted a supplemental New Drug Application (sNDA) for Xofluza™ (baloxavir marboxil) as a single-dose, oral treatment for people at high risk of complications from the flu. The Centers for Disease Control and Prevention (CDC) defines people at high risk for serious flu complications to include adults 65 years of age or older, or those who have conditions such as asthma, chronic lung disease, morbid obesity or heart disease. The FDA is expected to make a decision on approval by 4 November 2019.

"Influenza, or 'flu,' can be especially debilitating for people considered to be high risk, as they have an increased likelihood of serious complications, worsening of existing health problems and even hospitalisation or death," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "Xofluza is the first antiviral medicine to demonstrate a significant and clinically meaningful benefit in people at high risk of complications from the flu, for which there are currently no approved medicines."

The sNDA is based on results from the phase III CAPSTONE-2 study of a single dose of Xofluza compared with placebo or oseltamivir 75 mg, twice daily for five days, in people 12 years of age or older who are at high risk of complications from the flu.[1]

The FDA approved Xofluza in October 2018 for the treatment of acute, uncomplicated influenza in people 12 years of age or older. It is the first and only single-dose oral medicine approved to treat the flu, and the first new flu medicine with a novel proposed mechanism of action in nearly 20 years.

About CAPSTONE-2[1]
CAPSTONE-2 is a phase III multicentre, randomised, double-blind study that evaluated the efficacy and safety of a single dose of Xofluza compared with placebo and oseltamivir in 2,184 people 12 years of age or older who are at high risk of complications from the flu. The primary objective of the study evaluated the efficacy of a single dose of Xofluza compared with placebo by measuring the time to improvement of influenza symptoms. Important secondary endpoints compared outcomes in Xofluza versus placebo or oseltamivir, including time to resolution of fever, time to cessation of viral shedding, infectious virus detection in swabs of the nose and throat, prescription of antibiotics and influenza-related complications. The study, which was first presented in October 2018 at IDWeek, found that Xofluza:

- Significantly reduced the time to improvement of influenza symptoms versus placebo in people at high risk of complications from influenza (median time 73.2 hours versus 102.3 hours; $p<0.0001$);

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- Demonstrated superior efficacy (reduced time to improvement of influenza symptoms) versus placebo and oseltamivir in influenza type B (median time of 74.6 hours versus 100.6 hours and 101.6 hours, respectively (p=0.0138, p=0.0251);
- Demonstrated efficacy for secondary endpoints compared to placebo:
    - Significantly reduced the time to resolution of fever (median time of 30.8 hours versus 50.7 hours; p<0.0001), the incidence of influenza-related complications (2.8% versus 10.4%; p<0.05), the use of systemic antibiotics (3.4% versus 7.5%; p=0.01) and the length of time the virus continued to be released from the body (viral shedding; median time of 48 hours versus 96 hours; p<0.0001).
- Similar efficacy results were seen between Xofluza and oseltamivir for several secondary endpoints, but a significant difference was observed in the time to cessation of viral shedding favouring Xofluza:
    - No significant reduction in the time to resolution of fever (median time of 30.8 hours for Xofluza versus 34.3 hours for oseltamivir; p<0.2425), the incidence of influenza-related complications (2.8% for Xofluza versus 4.6% for oseltamivir; p=0.2558) and the use of systemic antibiotics (3.4% for Xofluza versus 3.9% for oseltamivir; p=0.8478).
    - Significantly reduced the length of time the virus continued to be released from the body (viral shedding; median time of 48 hours versus 96 hours; p<0.0001).

In CAPSTONE-2, Xofluza was well tolerated, with no safety signals identified. Xofluza had a numerically lower overall incidence of reported adverse events (25.1%) compared with placebo (29.7%) or oseltamivir (28.0%). The most common adverse events reported in the Xofluza group were bronchitis (2.9%), diarrhoea (2.7%), nausea (2.7%) and sinusitis (1.9%). The study was conducted globally 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 has demonstrated efficacy in a wide range of influenza viruses, including in vitro activity against oseltamivir-resistant strains and avian strains (H7N9, H5N1) in non-clinical studies.[2,3,4] 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.[2]

Xofluza will be further studied in a phase III development program 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 U.S.) and Shionogi & Co., Ltd. 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.

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.[5,6,7,8,9] 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 2018 employed about 94,000 people worldwide. In 2018, Roche invested CHF 11 billion in R&D and posted sales of CHF 56.8 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.

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