EU RISK MANAGEMENT PLAN FOR BALOXAVIR MARBOXIL/ XOFLUZA™

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 19 April 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
10-May-2024 11:00:24	Deputy QPPV	PPD
13-May-2024 18:53:23	Company Signatory (PV)	

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Rationale for Submitting an Updated RMP

This baloxavir marboxil European Union Risk Management Plan (EU RMP) Version 3.0 has been prepared to support the extension of the influenza treatment and post-exposure prophylaxis indications to include children aged 3 weeks and above.

Summary of Significant Changes in this RMP

- Part I: Product Overview was updated to include the new proposed indication and dosages.
- Part II Module SIII: Addition of pediatric study to clinical trial exposure.
- Part II Module SV: Post-authorization exposure was updated to align with the latest Period Benefit Risk Evaluation Report with the data lock point 22 February 2024. The table for Cumulative Exposure from Marketing Experience has been moved to Annex 7 and a reference to Annex 7 has been added in its place.
- Part VI: The indication was updated.
- Annex 7: The table for Cumulative Exposure from Marketing Experience has been moved from the core report to Annex 7. Summary tabulations of prospective and retrospective ICSRs on pregnancy from the most recent PBRER (with the 22 February 2024 data lock point) were updated.
- Annex 8: Summary of changes to the risk management plan over time was updated to reflect the changes made to this RMP.

Other RMP Versions Under Evaluation

N/A

Details of Currently Approved RMP

RMP Version Number: 2.0
Approved with Procedure: EMEA/H/C/004974/x0008

Date of Approval (opinion date): 10 November 2022

See page 1 for signature and date

Dr. PPD (Deputy EU QPPV) Date

See page 1 for signature and date

Dr. PPD Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Baloxavir marboxil
Pharmacotherapeutic group(s) (ATC Code)	J05AX25 (Other Anti-Virals)
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	XOFLUZA™
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: A potent and selective viral cap-dependent endonuclease inhibitor
	Summary of mode of action: Baloxavir inhibits transcription of influenza virus A and B by selective inhibition of CEN activity. The IC_{50} values of baloxavir against CEN activity for influenza A and B viruses ranged from 1.4 to 3.1 nmol/L and from 4.5 to 8.9 nmol/L, respectively.
	Important information about its composition: Baloxavir marboxil is a prodrug which is hydrolyzed by serine esterase in the intestine and liver to the active form, baloxavir.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: • Treatment of influenza: Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 1 year and above • Post-exposure prophylaxis of influenza: Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 1 year and above.
	Proposed: • Treatment of influenza: Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 3 weeks and above • Post-exposure prophylaxis of influenza: Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 3 weeks and above.

Table 1 Product Overview (Cont.)

Dosage in the EEA	Current: Treatment of influenza: A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours of symptom onset. Post-exposure prophylaxis of influenza: A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza. Baloxavir marboxil can be administered as tablets or granules for oral suspension. The recommended oral dose of baloxavir marboxil tablets depending on body weight is • <20 kg: Please refer to granules for oral suspension prescribing information • ≥20 kg to < 80kg: Single dose of 40mg taken as 1x 40mg tablet OR 2x 20mg tablets • ≥80kg: Single dose of 80mg taken as 1x 80mg tablet OR 2x 40mg tablets The recommended oral dose of baloxavir marboxil granules for oral suspension: • < 20 kg: 2 mg/kg • ≥ 20 kg – < 80 kg: 40 mg • ≥ 80 kg: 80 mg Xofluza may be taken with or without food.
	Proposed: Treatment of influenza: A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours of symptom onset. Post-exposure prophylaxis of influenza: A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza. Baloxavir marboxil can be administered as tablets or granules for oral suspension. The recommended oral dose of baloxavir marboxil depending on body weight is (adults, adolescents, children and infants (≥3 weeks of age): • <20 kg: 2mg/kg, as granules for oral suspension (refer to prescribing information)

	• ≥20 kg to < 80kg: Single dose of 40mg taken as 1x 40mg tablet OR 2x 20mg tablets OR 1 bottle granules for oral suspension • ≥80kg: Single dose of 80mg taken as 1x 80mg tablet OR 2x 40mg tablets OR 2 bottles granules for oral suspension
Pharmaceutical form(s) and strengths	Current: • 20 mg white to light yellow, oblong shaped film-coated tablets • 40 mg white to light yellow, oblong shaped film-coated tablets • 80 mg white to light yellow, oblong shaped film-coated • 2 mg/mL white to light yellow granules for oral suspension
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

CEN = cap-dependent endonuclease; EEA = European Economic Area, RMP = Risk Management Plan.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
ARDS	acute respiratory distress syndrome
AE	adverse event
$AUC_{0\text{-}24hr}$	area under the concentration-time curve from 0 to 24 hours
CDC	Centers for Disease Control (US)
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
ECDC	European Centre for Disease Prevention and Control (ECDC)
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HR	high-risk
M2	matrix 2
NAI	neuraminidase inhibitor
OwH	otherwise healthy
PA	polymerase acidic protein
PB1/2	polymerase basic protein 1/2
PEP	post-exposure prophylaxis
RMP	Risk Management Plan
RNA	ribonucleic acid
SmPC	Summary of Product Characteristics

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 INDICATION(S)

Incidence

Influenza is an acute respiratory infection caused by infection with influenza virus types A and B that occurs in outbreaks of varying severity almost every winter in temperate climates and year-round in tropical climates (Harmon et al. 2019, Tregoning et al. 2018). Influenza viruses are highly contagious with efficient person-person spread within communities and with the potential for pandemics with severe morbidity and mortality presenting significant public health challenges (Kalil and Thomas 2019, Scholtz et al. 2019, Sharma et al. 2019).

Influenza virus infection begins in the upper respiratory tract by inhalation of droplets from a sneeze or cough by an infected individual. Viruses replicate in ciliated columnar epithelial cells of the respiratory epithelium, releasing progeny viruses that spread to nearby cells (Kalil and Thomas 2019). Typically, symptomatic disease occurs 48 hours after exposure and the infectious virus can be isolated for 1 to 7 days with the peak of released virus occurring on the fourth or fifth day after infection in untreated individuals.

Influenza viruses enter the respiratory epithelial cell by attachment of the viral hemagglutinin to sialic acid-containing receptors on the cell membrane, followed by internalization of the virus into an acidic endosome (Bartoszko and Loeb 2019). In the acidic environment of the endosome, the hemagglutinin undergoes a conformational change that liberates a fusion peptide and results in fusion of the viral envelope with the endosomal membrane. At the same time, the third envelope protein, the matrix 2 (M2) protein, acts as an ion channel allowing hydrogen ions to enter the virion from the endosome. This acidification of the virion, in turn, allows the viral gene segments to leave the virion and enter the cytoplasm, a process known as uncoating.

Viral gene segments are transported to the nucleus, where the viral polymerase complex, composed of the proteins polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), and polymerase acidic protein (PA), directs the synthesis of the plus-sense messenger ribonucleic acid (RNA) and then the synthesis of new negative-sense viral RNA for incorporation into new virions. The polymerase proteins also play a role in disruption of host cell protein synthesis. After infection of cells and when replication begins, cell death of respiratory epithelium by several mechanisms, including necrosis and apoptosis, occurs (Bartoszko and Loeb 2019).

Prevalence

Influenza outbreaks occur virtually every year, although their extent and severity vary widely (Scholz et al. 2019). Both the US Centers for Disease Control (CDC) and the European Centre for Disease Prevention and Control (ECDC) have active surveillance

programs tracking potential outbreaks (https://www.cdc.gov/flu/weekly/usmap.htm and https://atlas.ecdc.europa.eu/public/index.aspx). Localized outbreaks, epidemics and pandemics take place at variable intervals (Uyeki et al. 2019). The most extensive and severe outbreaks are caused by influenza A virus, in part because of the remarkable propensity of the hemagglutinin and neuraminidase surface proteins of these viruses to undergo periodic antigenic variation. Major antigenic variations, called antigenic shifts, may be associated with pandemics and are restricted to influenza A virus. Minor variations are called antigenic drifts (Bartoszko and Loeb 2019, Sharma et al. 2019, Tregoning et al. 2018). Since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity.

Influenza A epidemics begin abruptly, peak over a 2- to 3-week period, generally last for 4 to 6 weeks, and often subside almost as rapidly as they began. The first indication of influenza activity in a community is an increase in the number of children with febrile respiratory illnesses who present for medical attention (Scholz et al. 2019). This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also rise at this time. In the temperate zones of the northern and southern hemispheres epidemics of influenza occur almost exclusively during the winter months. In those locations, it is highly unusual to detect influenza at other times, although serologic rises or even outbreaks have been noted rarely during warm-weather months. In contrast, influenza virus infections occur throughout the year in the tropics albeit at a comparatively low level.

Influenza B viruses can also co-circulate with influenza A viruses but are generally the minority type in any given season. Since the 2009 influenza pandemic, seasons with high influenza B virus circulation have occurred every two to three years (ECDC 2017). During the 2017–2018 season, both influenza type A and B viruses have co-circulated in the European region (WHO 2018a). Influenza B had been thought to be a milder virus compared to some strains of influenza A. In fact, multiple studies have suggested increased potency of influenza B virus in causing severe disease and mortality. Influenza B has been described to have significantly higher mortality rates compared to influenza A strains (Koutsakos et al. 2016, Sharma et al. 2019, van de Sandt et al. 2015).

The threat of influenza B has been recently recognized and acknowledged by the introduction of the quadrivalent vaccine that includes lineages of influenza A and B (Sharma et al. 2019, van de Sandt et al. 2015). These vaccines significantly decrease rates of infection; however, its effectiveness is disappointingly low in susceptible populations such as children within the age group of 9–17 years of age (28% effective) (Sharma et al. 2019). This indicates the limitation in our current vaccine strategies as well as the effectiveness of influenza B virus to spread in the susceptible school age

population, where simple protective measures such as hand hygiene and or masking one's cough may not be reliably practiced.

In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans.

Attack rates during seasonal outbreaks have been highly variable from outbreak to outbreak but most commonly are in the range of 10 to 20% of the general population (Paules and Subbarao 2017). Attack rates during pandemics are usually much higher. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50% in urban populations and that an additional 25% or more of individuals in these populations may have been subclinically infected with influenza A virus (Taubenberger and Morens 2009). Among institutionalized populations, and in semi closed settings with many susceptible individuals, even higher attack rates have been reported (Taubenberger and Morens 2009).

Demographics

Influenza can strike all sections of the population. Although morbidity and mortality are proportionately higher in the very young and the very old, the majority of infected cases occur in other age groups, by virtue simply of their greater numbers (Bartoszko and Loeb 2019, Kalil and Thomas 2019).

Although vaccination is the best strategy for the protection against influenza infection, particularly for patients at high risk for developing influenza-related complications, vaccination has been shown to be less effective in elderly patients (Bartoszko and Loeb 2019). This reduced effectiveness of vaccination in elderly patients is most likely due to the waning of the immune response with age known as "immune senescence", and presents an important, unmet challenge in this patient population.

While the condition is usually self-limiting in healthy adults, it can be associated with substantial morbidity and occasional mortality in children, the elderly, and the immunocompromised (Paules and Subbarao 2017). Children play a central role in the dissemination of influenza in the community by virtue of their relative sero-susceptibility and consequently higher illness attack rates. In addition to the acute illness, young children are at particular risk of secondary bacterial infections and complications. The most common complications of influenza in children are otitis media, conjunctivitis, gastrointestinal upset, pneumonia (primary influenza virus and secondary bacterial pneumonia), respiratory failure, and seizures. Other serious complications can also develop, including cardiac and neurological complications. Children develop more severe disease compared with adults, with higher hospitalization rates particularly in children aged ≤ 5 years (Rotrosen and Neuzil 2017).

In addition, health care workers with frequent exposure to patients are at high risk of acquiring influenza virus infection and when infected, of transmitting influenza to patients as well.

Main Existing Treatment Options

Influenza vaccination is the first line of defense against influenza. It can be administered to any person aged > 6 months (who does not have contraindications to vaccination) to reduce the likelihood of becoming ill with influenza. Trivalent and quadrivalent inactivated influenza vaccine can be used for any person aged > 6 months, including those with high-risk (HR) conditions. Live, attenuated influenza vaccine may be used for healthy, non-pregnant persons aged 2–49 years (Grohskopf et al. 2018). While vaccination clearly has a beneficial effect in reducing the impact of influenza in children, it is evident from the incidence figures and the calculations of vaccine efficacy that a broader therapeutic approach which includes antiviral agents is required to treat established infection (Bartoszko and Loeb 2019, Mameli et al. 2019, Uyeki et al. 2019).

Four antiviral drugs are currently approved in the EU for the prevention and treatment of influenza: the M2 ion-channel inhibitor amantadine and the neuraminidase inhibitors (NAIs) oseltamivir, zanamivir and peramivir. A second M2 inhibitor, rimantadine, holds marketing authorisations in the Czech Republic, France and Poland but is not marketed in these countries.

There is widespread resistance to amantadine and rimantadine in circulating seasonal influenza, and hence their use in clinical practice is very limited (Wang et al. 2013).

NAIs are the mainstay of treatment for influenza infections. Oseltamivir is indicated in children from birth for treatment and zanamivir is indicated from 5 years of age for treatment. However, both oseltamivir and zanamivir need to be administered twice daily for 5 days. In addition, the inhalation formulation of zanamivir can only be used in patients who are able to inhale the drug (excluding children aged < 5 years). There is also a risk of bronchospasm so caution needs to be exercised in prescribing zanamivir for patients with respiratory conditions such as chronic obstructive pulmonary disease (COPD) or asthma, patients for whom influenza treatment is especially important. Peramivir is an intravenous formulation and so is less suitable for use in otherwise healthy (OwH) patients or those presenting in an out-patient setting than available oral/inhalation formulations. New anti-influenza drugs with novel mechanisms of actions may help address these challenges.

Post-exposure prophylaxis (PEP) treatments are available but are not a substitute for influenza vaccination (Bartoszko and Loeb 2019, Mameli et al. 2019, Uyeki et al. 2019). Oseltamivir is indicated for individuals ≥1 year of age following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. Oseltamivir is administered once daily for 10 days following close contact with an infected individual. Oseltamivir is indicated for PEP of influenza in infants less than

1 year of age during a pandemic influenza outbreak. In addition, zanamivir is indicated for PEP from 5 years of age and is administered once daily for 10 days.

Risk Factors for the Disease

The CDC provides a complete list of people at high risk of developing influenza-related complications (CDC 2021). These characteristics make influenza in these patients a "potentially severe disease," which should be distinguished from the "common cold syndrome." The most prominent HR conditions are chronic cardiac and pulmonary diseases, and age (≥ 65 years and < 2 years). Primary influenza viral pneumonia is more common in individuals with cardiac disease, particularly those with congenital heart disease, congestive heart failure, coronary artery disease, diabetes, but has also been reported in OwH young adults as well as in older individuals with COPD and asthma (Bartoszko and Loeb 2019, Li et al. 2019, Kalil and Thomas 2019, Scholz et al. 2019).

Pregnant and postpartum women may be at increased risk for influenza associated complications (Chow et al. 2021). Influenza viral infection is also known to enhance host susceptibility to secondary bacterial infections (Raj et al. 2014). The most severe common complication of influenza infection is pneumonia, either primary viral or superimposed bacterial. Pregnancy increases the risk for severe disease, hospitalization, and mortality from influenza infection. Viral and bacterial pneumonias can be particularly aggressive, especially during pregnancy and the early postpartum period (Chow et al. 2021; Dawood et al. 2021; Dodds et al. 2007; Raj et al. 2014). Pregnant women in all 3 trimesters were at increased risk of influenza-associated complications, especially when early antiviral treatment was not started within the first 48 hours after symptom onset (Raj et al. 2014).

Natural History of the Indicated Condition in the (Untreated) Population

Morbidity and Mortality

The morbidity and mortality caused by seasonal influenza outbreaks continue to be substantial (Scholz et al. 2019, Sharma et al. 2019, Tregoning et al. 2018, Uyeki et al. 2019). Hospitalization and death occur mainly among HR groups. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths (WHO 2018b). Mortality in children varies across seasons and depends on viral subtype, pre-existing immunity and presence of underlying disease (Ruf and Knuf 2014). Recent estimates for children from 92 countries, the majority of whom were <5 years old, are 9,000–106,000 (median: 44,888) influenza-associated deaths annually (Iuliano et al. 2018).

The cost of primary care physician visits due to influenza for all EU 25 countries in 2005 was estimated at €267.2 million and the cost of hospital visits at €11.5 billion (Ryan et al. 2006). An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Secondary bacterial pneumonia can follow acute influenza. The most common bacterial pathogens in this setting are *Streptococcus*

pneumoniae, *Staphylococcus aureus* and *Haemophilus* influenza (Kalil and Thomas 2019). Mortality among individuals with chronic metabolic, renal, and certain immunosuppressive diseases has also been elevated, although lower than that among patients with chronic cardiopulmonary diseases. Pandemics provide the most dramatic evidence of the impact of influenza. However, illnesses that occur between pandemics account for greater total mortality and morbidity, albeit over a longer period.

Outcome of the (untreated) Target Disease

Illness caused by influenza is characterized by an abrupt onset of high fever, chills, prostration, fatigue, sore throat/pharyngitis, headache, myalgia, dry cough, rhinitis, cervical lymphadenopathy, and conjunctivitis. Conjunctivitis, rhinitis, and gastrointestinal symptoms are more common in infants and young children than in adults. Influenza infection severity can be defined as acute uncomplicated, referring to ambulant patients with a relatively benign self-limiting disease course, or “serious” or complicated infection requiring hospitalization (Scholz et al. 2019).

Through interplay between host immune defense and influenza virulent factors, the underlying disease can cause a wide spectrum of complications. The most significant complication of influenza is pneumonia: "primary" influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia (Kalil and Thomas 2019). Other pulmonary complications associated with influenza include worsening of COPD and exacerbation of chronic bronchitis or asthma and even acute respiratory distress syndrome (ARDS) (Harmon et al. 2019, Kalil and Thomas 2019). Sinusitis as well as otitis media (the latter occurring particularly often in children) may also be associated with influenza. In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur (Bartoszko and Loeb 2019). These include Reye's syndrome, myositis, rhabdomyolysis, and myoglobinuria. Although myalgias are very common in influenza, true myositis is rare. Myocarditis and pericarditis are rare. Electrocardiographic changes during acute influenza are common among patients with cardiac disease, but have been attributed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus (Scholz et al. 2019). Central nervous system (CNS) complications, including encephalitis and encephalopathy, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza infection (Bartoszko and Loeb 2019) with the influenza virus being considered as causal. Toxic shock syndrome associated with *S. aureus* or group A streptococcal infection following acute influenza infection has also been reported. In addition to complications involving the specific organ systems described above, influenza outbreaks include a number of cases in which elderly and other high-risk (HR) individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function – changes that occasionally are irreversible and lead to death. These fatalities contribute to the overall excess mortality associated with influenza A outbreaks (Paules and Subbarao 2017).

In OwH children, influenza is typically a mild to moderate disease and, in most children, resolves without complications. The most common signs and symptoms of influenza in children are sudden onset of fever, cough, and rhinorrhea (Poehling et al. 2006). Influenza is most severe in younger children (Peltola et al. 2003; Silvennoinen et al. 2009). Symptoms, such as sore throat, headache, myalgia, and fatigue, are reported less commonly in children than adults (Silvennoinen et al. 2009). Influenza can also present as croup, bronchiolitis, pneumonia, febrile disease mimicking bacterial sepsis. In addition, CNS, cardiac, muscle, or renal complications have been reported in children although they are not common (Peltola et al. 2003).

There are little data specifically focusing on epidemiology of infection in pregnant women, and there is no current evidence to suggest that pregnancy alters susceptibility to contracting influenza. Prevalence of influenza infection during pregnancy appears to be similar to that of the general population (Beigi 2014).

Due to normal changes of immunology, physiology, and anatomy during pregnancy, the body's ability to balance oxidative stress and prevent progression of influenza is impaired, increasing the risk of pregnant women to develop disease complications (Chow et al. 2021). Progesterone and glucocorticoids, which increase during pregnancy, can have an anti-inflammatory effect. This would explain the increase in severity of infectious agents such as influenza (Raj et al. 2014). The lower respiratory tract is altered due to the elevation of the diaphragm by up to 4 cm and a decrease in functional residual capacity. Functionally, there are changes in lung function, ventilation, and gas exchange, which lead to an increase in oxygen tension required for trans-placental oxygen transfer. Furthermore, changes in the cardiovascular system result in a decrease of pulmonary vascular resistance. All these physiological alterations might be further challenged by respiratory viral infections (van Riel et al. 2016).

Pneumonia in pregnancy from either bacterial or viral etiology can predispose to preterm birth. Previous data from 20th century pandemics suggested more specifically a fetal/ perinatal impact from maternal influenza infection (increased rates of preterm birth and miscarriage). Recent data have focused increasing attention to heightened rates of preterm birth but have also suggested a potential link between maternal influenza infection and fetal growth disturbances. Multiple investigations have found higher rates of small-for-gestational-age infants born to mothers infected with influenza (Beigi 2014).

Women who are up to 2 weeks postpartum may also be at increased risk of influenza-related complications as they transition back to normal physiology following pregnancy or pregnancy loss. Both observational data and animal models demonstrate that adverse birth outcomes may be increased following maternal influenza virus infection. This includes preterm delivery, low birth weight, congenital disease, miscarriage, and infant death (Meijer et al. 2015; Raj et al. 2014).

Transplacental influenza virus infection has been reported very rarely, and most adverse birth outcomes associated with maternal influenza virus infection are thought to be related to the severity of maternal illness (Chow et al. 2021, Rasmussen et al. 2012). The fetus appears to be rarely infected directly (Raj et al. 2014; Rasmussen et al. 2012).

Important Co-Morbidities

Complications of influenza occur most frequently in patients >64 years old and in those with certain chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression (Bartoszko and Loeb 2019, Li et al. 2019, Uyeki et al. 2019). Pregnancy in the second or third trimester also predisposes to complications with influenza (Mertz et al. 2019). Furthermore, residents of nursing homes and other long term facilities, people with weakened immune system due to disease or medications, people younger than 19 years old on chronic or long-term aspirin therapy, people with extreme obesity and people of American Indian and Alaskan Natives also are at higher risk for influenza complications (CDC 2021).

In children, underlying medical conditions, most commonly asthma, neurologic deficits, or malignancies, were identified in one-fourth of the children hospitalized with influenza A or B in a retrospective study (Peltola et al. 2002). Furthermore, a comparison of the estimated rates of hospitalization in children with acute respiratory disease during epidemics caused by respiratory viruses has shown that 61% of hospitalized children had an underlying condition that was pulmonary, and of these, 61% were diagnosed as asthma (Busse et al. 2010). This indicates that asthma is the most common underlying condition of children hospitalized with acute respiratory disease during influenza epidemics (CDC 2021).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage:

SII.1 TOXICITY

Repeat Dose Toxicity

Repeat-dose toxicity studies in rats and monkeys of up to 4 weeks daily oral administration did not reveal a relevant risk to humans.

Relevance to human usage: Not relevant to humans.

Hepatotoxicity

In repeat-dose oral toxicity studies in monkeys, elevated blood chemistry values were observed potentially suggesting hepatotoxicity. However, histopathological evaluation, including electron microscopic examinations, did not confirm the potential hepatotoxicity signal and did not show adverse liver changes even after 4 weeks daily dosing.

There were also no findings indicative of potential liver toxicity in rats.

Relevance to human usage: Since the signal from elevated blood chemistry parameters measured in monkeys were not confirmed in the histopathological examinations the findings are not considered to translate as a potential risk for hepatotoxicity in humans.

Discussion: In clinical trials, there were no clinically relevant differences in hepatic disorder adverse events (AEs) and liver function tests between baloxavir marboxil and placebo.

Reproductive/Developmental Toxicity

No effects on fertility were observed in rat studies performed with baloxavir marboxil. It has been confirmed in rats that the drug is excreted into milk (when dosed at 1 mg/kg) and is transferred to fetus via placenta. The pre- and postnatal study in rats did not show any drug-related adverse findings. Baloxavir marboxil did not cause malformations in rats or rabbits. In rabbits, a dose level of 1000 mg/kg/day (providing exposure equivalent to 14 times the human exposure based on the geometric mean area under the concentration-time curve from 0 to 24 hours [$AUC_{0\text{-}24hr}$] at the maximum recommended human dose of 80 mg in Phase III patients weighing at least 80 kg) caused maternal toxicity resulting in 2 miscarriages out of 19 pregnancies and an increased incidence of fetuses with a cervical rib skeletal variation, but no malformations. This minor skeletal variation is resorbed during the growing process of the adjacent cervical vertebra. A dose of 100 mg/kg/day in rabbits (providing exposure equivalent to 6 times the human exposure based on $AUC_{0\text{-}24hr}$) was without adverse effects. Therefore, it was concluded

that animal reproductive and developmental toxicity studies have not revealed a risk for humans.

Relevance to human usage: Animal reproductive and developmental toxicity studies have not revealed a risk for humans.

Juvenile Toxicity

Juvenile toxicity studies in rats dosed up to 1000 mg/kg/day did not show evidence of juvenile toxicity and thus did not reveal a risk.

Relevance to human usage: Animal juvenile toxicity studies have not revealed a risk for humans.

Genotoxicity

Baloxavir marboxil and the active metabolite, baloxavir, were negative in bacterial reverse mutation tests, micronucleus tests with cultured mammalian cells, and baloxavir marboxil was negative in an *in vivo* rodent micronucleus test. Thus, genotoxicity assays did not reveal a risk.

Relevance to human usage: Genotoxicity studies have not revealed a risk to humans.

SII.2 GENERAL SAFETY PHARMACOLOGY

There were no effects on the central nervous or respiratory systems in rats and no effects on blood pressure or electrocardiogram (ECG) in a cardiovascular monkey study.

Relevance to human usage: Safety pharmacology studies have not revealed a risk to humans.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

The current global clinical development with baloxavir marboxil consists of 22 completed studies: 12 Phase I, 1 Phase II, and 9 Phase III clinical studies. To date, 2930 patients and subjects have been exposed to baloxavir marboxil from the completed studies within the global clinical development program.

The exposure and safety data in this Risk Management Plan (RMP) are derived from the safety populations of the following completed clinical studies:

- Treatment Indication:
  - OwH treatment population:
    - Phase III Study 1601T0831 (hereafter referred to as T0831) in OwH patients with influenza aged ≥ 12 years
    - Phase II Study 1518T0821 (T0821) in OwH patients with influenza aged ≥ 20 years
    - Phase III Study CP40563 in OwH pediatric patients aged 1 < 12 years with influenza-like symptoms
    - Phase III Study 1618T0822 (T0822) in OwH pediatric patients with influenza aged 6 months < 12 years
    - Phase III Study 1705T0833 (T0833) in OwH pediatric patients with influenza and body weight <20 kg
    - Phase III Study 1813T0835 (T0835) in OwH pediatric patients with influenza aged < 12 years and weighing < 20 kg
    - Phase III Study CP40559 in OwH pediatric patients aged from birth to <1 year with influenza-like symptoms
  - HR treatment population:
    - Phase III Study 1602T0832 (T0832) in patients aged 12 and above with influenza who were at high risk of influenza complications.
- PEP indication:
  - Phase III Study 1719T0834 (T0834) in the post-exposure prophylaxis of influenza in adults and children (referred to as subjects).

An overview of the studies is provided in Table 2. It should be noted that multiple doses were evaluated in Study T0821 and therefore some patients received a lower than recommended dose (10 mg and 20 mg).

Table 2 Overview of Studies Contributing to the Safety Population

Study No.	Study Design	Dose and Regimen	No. Patients
Treatment Indication			
Otherwise Healthy Population			
1601T0831 (Phase III)	Multicenter (US and Japan), randomized, placebo / active control, double-blind study in adult and adolescent patients (12 to 64 years and ≥ 40 kg) with acute uncomplicated influenza	• Single dose of baloxavir marboxil tablet by body weight: ○ < 80 kg: 40 mg ○ ≥ 80 kg: 80 mg • Placebo • Oseltamivir: 75 mg BID for 5 days	**Randomized:** N = 1436 bxm: 612; pbo: 310; oselt.: 51 **Safety Population:** N = 1432 bxm: 610; pbo: 309; oselt.: 513
1518T0821 (Phase II)	Multicenter (Japan only), randomized, placebo-controlled double-blind study in adult patients (20 to 64 years) with acute uncomplicated influenza	• Single dose of baloxavir marboxil tablet: 10, 20, 40 mg or • Placebo	**Randomized:** N = 400 bxm: 300 (100 per dose group); pbo: 100 **Safety Population:** N = 400 bxm: 300 (100 per dose group); pbo: 100
CP40563 (Phase III)	Multicenter (global), randomized, double-blind, active-controlled study in OwH pediatric patients (1 to < 12 years) with influenza-like symptoms	• Single dose of baloxavir marboxil GfOS: ○ < 20 kg: 2 mg/kg ○ ≥ 20 kg: 40 mg • Oseltamivir (powder for oral suspension) BID for 5 days ○ ≤ 15 kg: 30 mg BID ○ > 15 kg to 23 kg:45 mg BID ○ > 23 kg to 40 kg:60 mg BID ○ > 40 kg: 75 mg BID	**Randomized:** N = 176 bxm: 117; oselt: 59 **Safety Population:** N = 173 bxm: 115; oselt: 58
1618T0822 (Phase III)	Multicenter (Japan only) open-label, non-controlled study in OwH pediatric patients (6 months to < 12 years) with acute uncomplicated influenza	• Single dose of baloxavir marboxil (10 and 20 mg tablets): ○ 5 to < 10 kg: 5 mg ○ 10 to < 20 kg: 10 mg ○ 20 to < 40 kg: 20 mg ○ ≥ 40 kg: 40 mg	**Enrolled:** N = 108 **Safety Population:** N = 107
1705T0833 (Phase III)	Multicenter (Japan only) open-label, non-controlled study in OwH pediatric patients (weighing <20 kg and aged <12 years) with acute uncomplicated influenza	• Single dose of baloxavir marboxil (2% granules): ○ < 10 kg: 1 mg/kg ○ 10 to < 20 kg: 10 mg	**Enrolled:** N = 33 **Safety Population:** N = 33
CP40559 (Phase III)	Multicenter (global) open-label, single-arm study in OwH pediatric patients (from birth to < 1 year) with influenza-like symptoms	• Single dose of baloxavir marboxil GfOS: ○ < 3 months: 1mg/kg ○ ≥ 3 months: 2mg/kg	**Enrolled: N = 49** **Safety Population: N = 48**

Table 2 Overview of Studies Contributing to the Safety Population (cont.)

Treatment Indication (continued)			
Otherwise Healthy Population (continued)			
1813T0835 (Phase III)	Multicenter (Japan only) open-label, non-controlled study in OwH pediatric patients (from birth to < 20 kg) with influenza	• Single dose of baloxavir marboxil (2% granules): ○ < 10 kg and < 3 months: 1 mg/kg ○ < 10 kg and ≥ 3 months: 2 mg/kg ○ 10 to < 20 kg: 20 mg	**Enrolled:** N = 45 **Safety Population:** N = 45
High Risk Population			
1602T0832 (Phase III)	Multicenter (global), randomized, placebo / active control, double-blind study in adults and adolescents (≥ 12 years and ≥ 40 kg) with acute uncomplicated influenza who are at high risk of developing influenza complications.	• Single dose of baloxavir marboxil tablet by body weight: ○ < 80 kg: 40 mg ○ ≥ 80 kg: 80 mg • Placebo • Oseltamivir: 75 mg BID for 5 days	**Randomized:** N = 2184[a] bxm: 730; pbo: 729; oselt.: 725 **Safety Population:** N = 2178 bxm: 730; pbo: 727; oselt.: 721
Post-exposure Prophylaxis Indication			
1719T0834 (Phase III)	Multicenter (Japan only), randomized, double-blind, parallel-group, placebo-controlled comparative study in subjects who are household members of influenza-infected index patients	• Single dose of baloxavir marboxil: ○ ≥ 12 years: ▪ < 80 kg: 40 mg ▪ ≥ 80 kg: 80 mg ○ < 12 years: ▪ < 10 kg: 1 mg/kg (2% granule), ▪ 10 to < 20 kg: 10 mg (2% granule), ▪ 20 to < 40 kg: 20 mg (tablet), or ▪ ≥ 40 kg: 40 mg (tablet) • Placebo	**Randomized:** N = 752 bxm: 375; pbo: 377 **Safety Population:** N = 749 bxm: 374; pbo: 375

BID = twice daily; bxm = baloxavir marboxil; GfOS = granules for oral suspension; oselt = oseltamivir; OwH = otherwise healthy; pbo = placebo.

[a] The actual number of patients randomized was 2184 patients, including 2 patients who were randomized twice in error; both patients were re-assigned to the oseltamivir group before dosing. Thus, a total of 2182 unique patients were randomized to treatment.

Duration of Exposure

Baloxavir marboxil is a single dose medicinal product. In all Phase II and III clinical studies that support the indications, single oral doses of baloxavir marboxil were administered to 2362 patients/subjects (Table 3). The following dosage forms of baloxavir marboxil were used:

- Tablets for all patients in Studies T0821, T0822, T0831, and T0832
- Granules 2% for all patients in Studies T0833 and T0835
- Granules for oral suspension 2mg/mL for all patients in Study CP40563 and Study CP40559
- Granules 2% for subjects weighing < 20 kg and tablets for subjects weighing ≥20 kg in Study T0834

Table 3 Duration of Exposure

Duration of Exposure	No. of Persons
Cumulative for All Indications	
1 day	2362 (100%)
Total All Indications	**2362 (100%)**
Treatment Indication	
Otherwise Healthy Population (Studies CP40563, CP40559, T0821, T0822, T0831, T0833 and T0835)	
1 day	1258 (100%)
Total Otherwise Healthy Population	**1258 (100%)**
High Risk Population (Study T0832)	
1 day	730 (100%)
Total High Risk Population	**730 (100%)**
PEP Indication (Study T0834)	
1 day	374 (100%)
Total PEP Indication	**374 (100%)**

Sources : Study T0821 (t_ex_dur_cv40814), Study T0831 (t_ex_dur_cv40815), T0832 (t_ex_dur_cv40818), T0834 (t_ex_dur_xv41428), Study CP40563 (t_ex_dur_cp40563), Study T0822 (t_ex_dur_cv40816), Study T0833 (t_ex_dur_cv40964), Study T0835 (t_ex_dur_xv41429), and Study CP40559 (t_ex_SE Study Drug Exposure, Safety-Evaluable Population).

PEP = post-exposure prophylaxis.

Exposure by Age Group and Gender

Within the overall safety population, the proportion of males (44.8% [1059/2362]) and females (55.2% [1303/2362]) treated with baloxavir marboxil is broadly similar across all indications (Table 4). The majority of patients were adults aged 18 – 64 years (68.5% [1617/2362]).

Table 4 Age Group and Gender

Age Group	Male	Female	Total
Cumulative for All Indications			
0 – 27 days	1 (0.1%)	0	1 (0.1%)
28 days – 23 months	43 (4.1%)	41 (3.1%)	84 (3.6%)
2 – 11 years	162 (15.3%)	172 (13.2%)	334 (14.1%)
12 – 17 years	58 (5.5%)	51 (3.9%)	109 (4.6%)
18 – 64 years	687 (64.9%)	930 (71.4%)	1617 (68.5%)
65 – 74 years	77 (7.3%)	83 (6.4%)	160 (6.8%)
75 – 84 years	31 (2.9%)	23 (1.8%)	54 (2.3%)
≥ 85 years	0	3 (0.2%)	3 (0.1%)
Total All Indications	**1059 (100%)**	**1303 (100%)**	**2362 (100%)**
Treatment Indication			
Otherwise Healthy Population (Studies CP40563, CP40559, T0821, T0822, T0831, T0833, and T0835)			
0 – 27 days	1 (0.2%)	0	1 (0.1%)
28 days – 23 months	42 (6.4%)	41 (6.8%)	83 (6.6%)
2 – 11 years	129 (19.8%)	135 (22.3%)	264 (21.0%)
12 – 17 years	41 (6.3%)	35 (5.8%)	76 (6.0%)
18 – 64 years	440 (67.4%)	394 (65.1%)	834 (66.3%)
Total Otherwise Healthy Population	**653 (100%)**	**605 (100%)**	**1258 (100%)**
High Risk Population (Study T0832)			
12 – 17 years	13 (4.0%)	8 (2.0%)	21 (2.9%)
18 – 64 years	208 (63.2%)	292 (72.8%)	500 (68.5%)
65 – 74 years	77 (23.4%)	78 (19.5%)	155 (21.2%)
75 – 84 years	31 (9.4%)	21 (5.2%)	52 (7.1%)
≥ 85 years	0	2 (0.5%)	2 (0.3%)
Total High Risk Population	**329 (100%)**	**401 (100%)**	**730 (100%)**
PEP Indication (Study T0834)			
28 days – 23 months	1 (1.3%)	0	1 (0.3%)
2 – 11 years	33 (42.9%)	37 (12.5%)	70 (18.7%)
12 – 17 years	4 (5.2%)	8 (2.7%)	12 (3.2%)
18 – 64 years	39 (50.6%)	244 (82.2%)	283 (75.7%)
65 – 74 years	0	5 (1.7%)	5 (1.3%)
75 – 84 years	0	2 (0.7%)	2 (0.5%)
≥ 85 years	0	1 (0.3%)	1 (0.3%)
Total PEP Indication	**77 (100%)**	**297 (100%)**	**374 (100%)**

Table 4 Age Group and Gender (cont.)

Percentages are based on column subtotals.

Sources: Study T0821 (t_ex_age_sex_cv40814), Study T0831 (t_ex_age_sex_cv40815), T0832 (t_ex_age_sex_cv40818), and T0834 (t_ex_age_sex_xv41428), Study CP40563 (t_ex_age_sex_cp40563), Study T0822 (t_ex_age_sex_cv40816), Study T0833 (t_ex_dur_cv40964), Study T0835 (t_ex_age_sex_xv41429), and Study CP40559 (t_dm_SE Demographics and Baseline Characteristics, Safety-Evaluable Population).

PEP = post-exposure prophylaxis.

Exposure by Dose Received

With the exception of Study T0821, patients in all studies received a single dose with the dose based on body weight and age (see Table 2). Overall, the majority of patients/subjects received a 40 mg or 80 mg single dose of baloxavir marboxil (77.2% [1823/2362]) (Table 5).

Table 5 Extent of Exposure by Dose Received

Dose	No. of Persons
Cumulative for All Indications	
4 mg	8 (0.3%)
5 mg	8 (0.3%)
6 mg	1 (0.0%)
7 mg	5 (0.2%)
8 mg	5 (0.2%)
9 mg	2 (0.1%)
10 mg	172 (7.3%)
12 mg	9 (0.4%)
14 mg	9 (0.4%)
16 mg	14 (0.6%)
18 mg	9 (0.4%)
20 mg	260 (11.0%)
24 mg	3 (0.1%)
26 mg	5 (0.2%)
28 mg	5 (0.2%)
30 mg	2 (0.1%)
32 mg	6 (0.3%)
34 mg	4 (0.2%)
36 mg	5 (0.2%)
38 mg	7 (0.3%)
40 mg	1352 (57.2%)
80 mg	471 (19.9%)
Total All Indications	**2362 (100%)**
Treatment Indication	
Otherwise Healthy Population (Studies CP40563, CP40559, T0821, T0822, T0831, T0833 and T0835)	
4 mg	8 (0.6%)
5 mg	8 (0.6%)
6 mg	1 (0.1%)
7mg	5 (0.4%)
8 mg	5 (0.4%)
9 mg	2 (0.2%)
10 mg	153 (12.2%)
12 mg	9 (0.7%)
14 mg	9 (0.7%)

Table 5 Extent of Exposure by Dose Received (cont.)

Otherwise Healthy Population (continued)	
16mg	14 (1.1%)
18mg	9 (0.7%)
20mg	212 (16.9%)
24mg	3 (0.2%)
26mg	5 (0.4%)
28 mg	5 (0.4%)
30 mg	2 (0.2%)
32 mg	6 (0.5%)
34 mg	4 (0.3%)
36 mg	5 (0.4%)
38 mg	7 (0.6%)
40 mg	643 (51.1%)
80 mg	143 (11.4%)
Total Otherwise Healthy Population	**1258 (100%)**
High Risk Population (Study T0832)	
40 mg	419 (57.4%)
80 mg	311 (42.6%)
Total High Risk Population	**730 (100%)**
PEP Indication (Study T0834)	
10 mg	19 (5.1%)
20 mg	48 (12.8%)
40 mg	290 (77.5%)
80 mg	17 (4.5%)
Total PEP Indication	**374 (100%)**

Sources: Study T0821 (t_ex_dose_cv40814), Study T0831 (t_ex_dose_cv40815), T0832 (t_ex_dose_cv40818), and T0834 (t_ex_dose_xv41428), Study CP40563 (t_ex_dose_rmp_cp40563), Study T0822 (t_ex_dose_cv40816), Study T0833 (t_ex_dose_cv40964), Study T0835 (t_ex_dose_xv41429), and Study CP40559(t_ex_SE Extent of Exposure by Dose Received (Safety Population - CP40559)).

PEP = post-exposure prophylaxis.

Exposure by Ethnic Origin

Within the overall safety population, the majority of patients/subjects were not of Hispanic or Latino descent (81.8%) (Table 6).

Table 6 Extent of Exposure by Ethnic Origin

Ethnic Origin	No. of Persons
Cumulative for All Indications	
Hispanic or Latino	416 (17.6%)
Not Hispanic or Latino	1932 (81.8%)
Unknown	9 (0.4%)
Not Reported	5 (0.2%)
Total All Indications	**2362** (**100**%)
Treatment Indication	
Otherwise Healthy Population (Studies CP40563, CP40559, T0821, T0822, T0831, T0833 and T0835)	
Hispanic or Latino	183 (14.5%)
Not Hispanic or Latino	1064 (84.6%)
Unknown	9 (0.7%)
Not Reported	2 (0.2%)
Total Otherwise Healthy Population	**1258** (**100**%)
High Risk Population (Study T0832)	
Hispanic or Latino	233 (31.9%)
Not Hispanic or Latino	494 (67.7%)
Not Reported	3 (0.4%)
Total High Risk Population	**730** (**100**%)
PEP Indication (Study T0834)	
Not Hispanic or Latino	374 (100%)
Total PEP Indication	**374** (**100**%)

Sources: Study T0821 (t_ex_ethnic_cv40814), Study T0831 (t_ex_ethnic_cv40815), T0832 (t_ex_ethnic_cv40818), and T0834 (t_ex_ethnic_xv41428), Study CP40563 (t_ex_ethnic_cp40563), Study T0822 (t_ex_ethnic_cv40816), Study T0833 (t_ex_ethnic_cv40964), Study T0835 (t_ex_ethnic_xv41429), and Study CP40559 (t_dm_SE Demographics and Baseline Characteristics, Safety-Evaluable Population).

PEP = post-exposure prophylaxis.

Exposure by Race

Within the overall safety population, the majority of patients/subjects were Asian (60.3%) followed by White (32.0%) (Table 7).

Table 7 Extent of Exposure by Race

Race	No. of Persons
Cumulative for All Indications	
American Indian Or Alaska Native	9 (0.4%)
Asian	1424 (60.3%)
Black Or African American	144 (6.1%)
Multiple	4 (0.2%)
Native Hawaiian Or Other Pacific Islander	1 (0.0%)
White	757 (32.0%)
Other	23 (1.0%)
Total All Indications	**2362** (**100**%)
Treatment Indication	
Otherwise Healthy Population (Studies CP40563, CP40559, T0821, T0822, T0831, T0833, and T0835)	
American Indian Or Alaska Native	2 (0.2%)
Asian	849 (67.5%)
Black Or African American	72 (5.7%)
Multiple	4 (0.3%)
White	317 (25.2%)
Other	14 (1.1%)
Total Otherwise Healthy Population	**1258** (**100**%)
High Risk Population (Study T0832)	
American Indian Or Alaska Native	7 (1.0%)
Asian	201 (27.5%)
Black Or African American	72 (9.9%)
Native Hawaiian Or Other Pacific Islander	1 (0.1%)
White	440 (60.3%)
Other	9 (1.2%)
Total High Risk Population	**730** (**100**%)
PEP Indication (Study T0834)	
Asian	374 (100%)
Total PEP Indication	**374** (**100**%)

Table 7 Extent of Exposure by Race (cont.)

Sources: Study T0821 (t_ex_race_cv40814), Study T0831 (t_ex_ race_cv40815), T0832 (t_ex_race_cv40818), and T0834 (t_ex_ race_xv41428), Study CP40563 (t_ex_race_cp40563), Study T0822 (t_ex_race_cv40816), Study T0833 (t_ex_race_cv40964), Study T0835 (t_ex_race_xv41429), and Study CP40559 (t_dm_SE Demographics and Baseline Characteristics, Safety-Evaluable Population).

PEP = post-exposure prophylaxis

PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 8 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Exclusion Criteria Relevant for All Indications			
Women who were pregnant or within 2 weeks post-partum*	Common exclusion criteria in clinical trials, intended to prevent the possibility of any harmful effects to the fetus/baby resulting from exposure to IMP while reproductive toxicology and safety data is relatively limited.	No	No adverse clinical outcomes are anticipated should baloxavir marboxil be used during pregnancy based on animal reproductive and developmental toxicity studies. Furthermore, Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises against the use of baloxavir marboxil during pregnancy, unless the potential benefit for the mother outweighs the potential risk to the fetus.
Women who were breastfeeding	Common exclusion criteria in clinical trials, intended to prevent the possibility of any harmful effects to the baby during IMP development.	No	It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk. When dosed at 1 mg/kg, baloxavir marboxil or its metabolites are secreted in the milk of lactating rats. A risk to the newborns/infants cannot be excluded. Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises that the potential benefit of baloxavir marboxil to the nursing mother and the potential risk to the infant should be taken into account.

Table 8 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Exclusion Criteria Relevant for Treatment Indication			
Patients who had a severe influenza virus infection requiring inpatient treatment.	The pivotal studies were designed to assess the safety and efficacy of baloxavir marboxil in patients with acute uncomplicated influenza	No	A study of baloxavir marboxil in combination with standard-of-care neuraminidase inhibitors in hospitalized patients with severe influenza was completed.
Adult and adolescent patients with influenza who weighed < 40 kg	The comparator drug in treatment studies, oseltamivir, requires a dose modification in patients less than 40 kg which could not be implemented in a double blind, randomized study.	No	No difference in safety profile as compared to an otherwise healthy patient is expected based on scientific evidence.

* Based on the definitions of people at high risk by the Centers for Disease Control and Prevention (CDC)

SmPC = Summary of Product Characteristics; IMP = investigational medicinal product.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for baloxavir marboxil is unlikely to detect certain types of adverse drug reactions (ADR) such as rare adverse reactions or reactions caused by cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 9 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	8 patients with moderate hepatic impairment were assessed in Study 1611T081B 2 patients with abnormal hepatic function were exposed to baloxavir marboxil in Study T0832 4 subjects with abnormal hepatic function were exposed to baloxavir marboxil in Study T0834
Patients with renal impairment	10 patients with chronic kidney disease and 2 patients with renal failure were exposed to baloxavir marboxil in Study T0832
Patients with cardiovascular impairment	83 patients with heart disease were exposed to baloxavir marboxil in Study T0832
Immunocompromised patients	27 immunocompromised patients were exposed to baloxavir marboxil in Study T0832
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Included in the clinical development program (see Table 6)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other:	Not included in the clinical development program

Note: Individual patients/subjects could have more than one comorbidity.

Use in Pregnancy and Lactation

Due to normal changes of immunology, physiology, and anatomy during pregnancy, the body's ability to balance oxidative stress and prevent progression of influenza is impaired, increasing the risk of pregnant women to develop disease complications (Chow et al. 2021). The World Health Organization, ECDC, American College of Obstetricians and Gynecologists, Infectious Disease Society of America, and the US

CDC recommend antivirals for the treatment of pregnant and postpartum women with influenza (Chow et al. 2021).

Pregnant and lactating women were excluded from clinical trials with baloxavir marboxil. The IBM MarketScan® Commercial Claims and Encounters Database was utilized to determine if there was any real-world data on the use of baloxavir marboxil in pregnant women in the U.S. This database contains insurance claims information for a sample of US patients under 65 years of age in private-sector plans; as of 2017, approx. 26 million patients were captured in the database. The aim was to look at hospitalizations within 14 days of pharmacy fill for a prescription for Xofluza.

Pregnancy was approximated by using delivery data and estimating a 40-week window prior to delivery date, so there is possible measurement error in the exact pregnancy start dates used in this analysis. The analysis was restricted to patients ages 12 to 55 (inclusive), and patients with at least 6 months of continuous enrollment prior to pregnancy.

Based on this database, a total of 2,243 pregnant patients with at least 1 influenza episode during their pregnancy were identified during the 2018-19 influenza season in the US. Only 7 (0.31%) of these pregnant patients had a pharmacy fill for Xofluza. A total of 655 pregnant patients with at least 1 influenza episode during their pregnancy were identified during the 2019-20 influenza season. Only 1 (0.15%) pregnant patient had a pharmacy fill for Xofluza.

As noted above, in general antiviral treatment is recommended for pregnant patients and is considered effective at reducing the risk of adverse pregnancy outcomes. However, although the non-clinical data available for baloxavir marboxil does not indicate any safety concerns associated with pregnant or lactating women, the low number of pregnancies exposed to baloxavir marboxil specifically remain too small to draw conclusions. At this time alternative antiviral treatments for influenza are available that do have sufficient data to suggest safe use in pregnant and lactating women.

The detailed evaluation of pregnancy and lactation cases with baloxavir marboxil available to the marketing authorization holder (MAH) is presented in Periodic Benefit Risk Evaluation Report 1129203 (reporting interval 23 February 2023 to 22 February 2024) in Section 15.2. Interval and cumulative data of the pregnancy outcome (Overall Exposure, Exposure by Parents [mother and father], and Exposure by Source) is presented in Annex 7 of the RMP.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

During the period of 23 February 2018 through 22 February 2024, an estimated cumulative total of 17,875,914 patients have received baloxavir marboxil from marketing experience (see Annex 7.)

SV.1.1 Method Used to Calculate Exposure

US Data

The estimated number of patients treated with baloxavir marboxil is based on U.S. treatment dataset (third party dataset tracking prescription medicines usage in United States). The following metrics are not captured:

- Product dispensed through hospital in-patient pharmacies.

Japan Data

The estimated number of patients treated with baloxavir marboxil is based on Japan sales data provided by the Shionogi team. The demographic stratification is also provided by the Shionogi team.

Taiwan Data

The estimated number of patients treated with baloxavir marboxil is directly provided by the Shionogi team. The demographic stratification used for Taiwan is same as that used for Japan.

Serbia Data

The estimated number of patients treated with baloxavir marboxil is based on the sales data provided by Hemofarm. Demographic stratification not available.

EEA and Rest of World Data (including China and European Union)

The estimated number of patients treated with baloxavir marboxil is based on internal sales data (quantity distributed to wholesalers). Demographic stratification data is limited so stratification provided has been informed by using U.S. Trx dataset.

PART II: MODULE SVI—ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The pharmacological action of baloxavir marboxil is limited to inhibition of viral cap-dependent endonuclease activity. It has no other pharmacological activity. Based on non-clinical studies, baloxavir marboxil does not penetrate into the central nervous system. Overall, there is no abuse potential for illegal purposes.

PART II: MODULE SVII—IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

No identified or potential risks were detected.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for NOT including an identified or potential risk in the list of safety concerns in the RMP:

The overall safety profile of baloxavir marboxil is based on data of 22 completed Phase I–III clinical studies. No ADRs were identified from:

- Individual studies or based on combined AE data from 3 placebo-controlled clinical studies in adult and adolescent patients with influenza (Studies T0821, T0831 and T0832) with a total of 1440 patients receiving baloxavir marboxil (40 mg and 80 mg dose groups only)
- OwH pediatric patients with influenza with a total of 348 patients receiving baloxavir marboxil (Studies CP40563, T0822, T0833, T0835 and CP40559)
- Subjects of all ages in a PEP setting with 374 subjects receiving baloxavir marboxil (Study T0834).

Overall, this includes OwH children, adolescents and adults, adolescents and adult patients at high risk of developing complications associated with influenza (e.g., elderly patients and patients with chronic cardiac or respiratory disease), and subjects of all ages judged not to have influenza virus infection who live with an influenza-infected index patient.

Post-marketing activities identified a safety signal related to hypersensitivity reactions (including anaphylaxis). Following a full evaluation, the Applicant included hypersensitivity reactions (including anaphylaxis/anaphylactic reactions and less severe forms including urticaria and angioedema) as an ADR in the Summary of Product Characteristics (SmPC). The Applicant will continue to monitor such events through routine pharmacovigilance activities and does not consider this to fulfil the criteria of an important identified risk as no specific risk management and clinical measures beyond

labeling are proposed. Based on the evaluation of all data received to date, the Applicant concludes that the benefit-risk profile of baloxavir marboxil continues to remain positive.

In summary, due to the lack of any important identified or potential risks for baloxavir marboxil from the populations studied in the clinical development program, or from post marketing surveillance, it is considered that the further characterization of the safety profile can be assessed through routine signal detection and adverse reaction reporting.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

To date, no risks have been identified which fulfil the criteria of inclusion in the list of safety concerns in the RMP.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

There are no new safety concerns for presentation in this version of the RMP.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

No important identified risks have been identified.

Information on Important Potential Risks

No important potential risks have been identified.

SVII.3.2. Presentation of the Missing Information

No missing information has been identified.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 10 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection for baloxavir marboxil.

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

Specific adverse reaction follow-up questionnaires: Not applicable

Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding:

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the Applicant to be sufficient to obtain and analyze relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 11 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Not applicable				

CHMP= Committee for Medicinal Products for Human Use; NCA=National Competent Authority; PRAC=Pharmacovigilance Risk Assessment Committee

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Not applicable. There are no post-authorization efficacy studies for baloxavir marboxil.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN

V.1 ROUTINE RISK-MINIMIZATION MEASURES

No important identified or potential risks are identified with the use of baloxavir marboxil; therefore, this section is not applicable.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Based on the current safety profile of baloxavir marboxil, no additional risk minimization activities are deemed necessary.

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Not applicable

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR XOFLUZA™ (BALOXAVIR MARBOXIL)

This is a summary of the risk-management plan (RMP) for *Xofluza*. The RMP details important risks of *Xofluza,* how these risks can be minimized, and how more information will be obtained about *Xofluza*'s risks and uncertainties (missing information).

Xofluza's (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Xofluza* should be used.

This summary of the RMP for *Xofluza* should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of *Xofluza's* RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 3 weeks and above and for post-exposure prophylaxis of influenza in individuals aged 1 and above (see SmPC for the full indication). It contains *baloxavir marboxil* as the active substance, and it is given orally.

Further information about the evaluation of *Xofluza's* benefits can be found in *Xofluza's* EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of *Xofluza*, together with measures to minimize such risks and the proposed studies for learning more about *Xofluza*'s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status — The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of *Xofluza* are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Xofluza*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	*none*
Important potential risks	*none*
Missing information	*none*

II.B Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for baloxavir marboxil.

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of *Xofluza*.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for *Xofluza.*

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not applicable