swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Xofluza

International non-proprietary name: baloxavir marboxil
Pharmaceutical form: film-coated tablet
Dosage strength(s): 20 mg, 40 mg, 80 mg
Route(s) of administration: oral
Marketing authorisation holder: Roche Pharma (Schweiz) AG
Marketing authorisation no.: 67426
Decision and decision date: approved on 4 October 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

(Approved indication / *requested extension of indication*)

Treatment of influenza
Xofluza is indicated for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours and who are:

- adults and paediatric patients *1 year of age and older*, who are otherwise healthy*,*
  or
- adolescent patients 12 years of age and older and adults who are at high risk of developing influenza-related complications

Influenza post-exposure prophylaxis
Post-exposure prophylaxis of influenza in patients *1 year of age and older.*

2.2.2 Approved indication

Treatment of Influenza
Xofluza is indicated for the treatment of uncomplicated influenza in patients who have been symptomatic for no more than 48 hours:

- For children aged 1 year and above and adults that are otherwise healthy
  or
- For children aged 12 years and above and adults that are at high risk of developing influenza-related complications

Post-exposure prophylaxis of influenza
Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 1 year and above.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Treatment and post-exposure prophylaxis:

- for paediatric patients with a body weight ≥ 40 kg, no change to the dosage recommendation was requested
- for paediatric patients with a body weight ≥ 20 kg and < 40 kg: 40 mg as a single dose
- for paediatric patients with a body weight < 20 kg: 2 mg per kg body weight as a single dose.

Xofluza, granules for oral suspension, is intended for patients or individuals aged 1 to 12 years.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 September 2022
Formal objection	14 October 2022
List of Questions (LoQ)	8 March 2023
Response to LoQ	23 April 2023
Preliminary decision	22 June 2023
Response to preliminary decision	15 August 2023
Final decision	4 October 2023
Decision	approval

3 Medical context

Influenza is caused by influenza A and influenza B viruses. There are various subtypes of the A viruses and 2 lineages of the B viruses: Victoria and Yamagata. Influenza virus is transmitted by direct or indirect contact with virus-containing respiratory fluids.

Symptoms of influenza include fever, chills, coughing, sore throat or difficulty swallowing, headache, joint and muscle pain, runny nose, dizziness, and a loss of appetite. Possible complications include upper respiratory tract infections, pneumonia, and secondary bacterial infections. Pregnant women, premature newborns, the elderly and people with certain chronic diseases are at increased risk of complications from influenza.

In Switzerland, influenza results in approximately 112,000 to 275,000 doctor's consultations, several thousand hospitalisations due to complications, and several hundred deaths every year (for detailed data on seasonal flu, please refer to the website of the Federal Office of Public Health).
The risk of seasonal influenza infection can be reduced by the use of influenza vaccines.

4 Nonclinical aspects

The nonclinical documentation submitted with the initial marketing authorisation application supports the approval of Xofluza® (baloxavir marboxil) for the applied indication extensions in the paediatric population.

No new nonclinical studies were conducted to support the requested extension of the indication. This was considered acceptable since the changes with regard to posology and method of administration were adapted for the paediatric population based on clinical studies.

Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

Pharmacokinetics

Paediatric treatment

To describe the PK profile of baloxavir following oral dosing of baloxavir marboxil in adult, adolescent, and paediatric patients infected with influenza, a population PK model was developed based on data from the 3 clinical studies conducted in Asian and/or non-Asian adult and adolescent patients and 3 clinical studies conducted in Asian and non-Asian paediatric patients.

The concentration-time profiles of baloxavir were best described by a 2-compartment disposition model with first-order absorption and elimination processes. The full covariate approach retained race effect (Asian/non-Asian) on Q/F, age and gender effects on Ka, and gender effect on F_{rel}, in addition to body weight effects on the clearance and volume parameters, as well as the race effects (Asian/non-Asian) on CL/F and Vc/F already included in the base model. Overall, the performance of the final model was adequate. Simulations confirmed the impact of race and body weight on baloxavir exposures identified in the population PK analysis submitted and evaluated as part of the initial MAA of Xofluza.

Using the population PK model, the Bayesian estimates of the PK parameters were derived to compare the baloxavir exposures in non-Asian paediatric patients to those in non-Asian adolescent and adult patients.

The values for $AUC_{0\text{-}inf}$ in paediatrics were comparable between those observed in the 40 mg and 80 mg dose groups in adult and adolescent patients. There was a trend of higher maximum concentrations in paediatric patients. Bayesian estimates of the PK parameters in the paediatric studies confirmed the known impact of race on baloxavir exposures.

Overall, the proposed dosing regimen for paediatric patients (1 to <12 years), i.e. 2 mg/kg of baloxavir marboxil granules in patients weighing <20 kg and 40 mg of baloxavir marboxil granules in patients weighing ≥20 kg, leads to comparable exposures to those observed in adolescents and adults. See “Efficacy” for the assessment of the validity of the PK bridging.

Post-exposure prophylaxis

To support the extension of indication for post-exposure prophylaxis, PK and PD data were collected in a pivotal Phase 3 study. Since the Phase 3 study was conducted in Japan and, thus, the paediatric patients did not receive the proposed dose, the extrapolation of the efficacy results to non-Asian subjects was based on PK bridging.

Overall, the observed baloxavir plasma concentrations were slightly higher in subjects ≥12 years when compared with subjects <12 years. In subjects <12 years baloxavir plasma concentrations were similar across body weight categories. However, the majority of subjects (approximately 80%) were ≥12 years of age. These findings were confirmed by the Bayesian-estimated PK parameters using the previously developed population PK model.

Successful bridging based on 3 steps:

- Different indications did not have an impact on the baloxavir PK in adult/adolescent and paediatric Asian subjects; thus, the same is expected for non-Asian patients.
- In an exploratory graphical exposure-response analysis, no exposure differences were observed between the subjects who met the primary (PEP failure) and secondary endpoints and those who did not.
- Simulations using the actual doses administered suggest comparable baloxavir concentrations across race, body weight, and dosing regimen.

Due to the body weight-based dosing, comparable baloxavir exposures are expected between Asian and non-Asian paediatric patients. In contrast, the baloxavir concentrations tend to be higher in Asian adults/adolescent patients compared to those in non-Asian adults/adolescent patients, which is expected considering the known impact of race and that the same dose is administered.

Pharmacodynamics

Graphical exploration of the exposure-response relationship revealed that there is no difference in time to alleviation of influenza signs and symptoms (TTAS) between patients with low and high baloxavir exposure. No difference in AE incidence was observed between patients with low and high baloxavir exposure.

5.2 Dose finding and dose recommendation

No formal dose-finding studies were performed. Paediatric dosing was based on modelling and simulations to match exposure (AUC_{inf}, C_{24}, C_{72}) in adults (see “Clinical pharmacology”).

Safety and tolerability of these doses were evaluated in Phase 3 studies CP40563 and 1719T0834, which also provided supportive data on efficacy. This partial extrapolation approach is in line with FDA guidance (Influenza: developing drugs for treatment and/or prophylaxis, 2011) and can be accepted.

5.3 Efficacy

The extension of the indication applied for was supported by data from the pivotal Phase 3 studies CP40563 (miniSTONE-2, treatment of influenza) and 1719T0834 (BLOCKSTONE, post-exposure prophylaxis of influenza) as well as supporting data from 2 non-controlled single-arm Phase 3 studies conducted in Japan (T0822 and T0833, both for treatment of influenza). These were in part assessed in a previous application (please refer to the information for healthcare professionals for details of the pivotal studies). For the treatment indication, CP40563 showed that in the otherwise healthy 1 to 12 years age group, the effect of baloxavir marboxil in terms of time to alleviation of influenza signs and symptoms was comparable to the active comparator oseltamivir, and the incidence of influenza-related complications was low and similar in both treatment groups. Heterogenicity in the efficacy endpoint of time to alleviation of symptoms between studies was addressed when the more subjective evaluation factor “return to normal health and activity” was removed (keeping e.g. cough, nasal symptoms, body temperature). In study 1719T0834, for post-exposure prophylaxis, efficacy was shown in the 1 to 12 years age group. The number of very young patients (1 to 3 years) is limited but PK modelling has shown similar exposure in children down to 1 year of age, and it has been accepted that efficacy can be extrapolated from adolescent and adult data.

In addition, the applicant newly submits the supportive study T0835, which was the focus of the present application. This was an open-label non-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of baloxavir marboxil in healthy paediatric patients with influenza. A total of 45 patients received 1 dose of baloxavir marboxil granules at doses of 14 mg (1 patient, 2.2%), 16 mg (6 patients, 13.3%), 18 mg (2 patients, 4.4%), and 20 mg (36 patients, 80.0%). The median age was 3.0 years (range 0 to 6 years), 19 patients (44.2%) were female, and all patients were of Asian race. The median body weight at screening was 14.3 kg (range 7.4 to 19.8 kg). The most prevalent subtype was A/H3 (22 patients, 51.2%), followed by A/H1N1 (10 patients, 23.3%), and type B (10 patients, 23.3%). One patient (2.3%) had a mixed infection.

In the overall intention to treat infected (ITTI) population, the primary endpoint median time to alleviation of influenza illness was 37.8 hours (95% CI: 27.5, 46.7). In study T0835, of the 39 patients with available pre- and post-dose sequencing results, a total of 16 patients (41.0%) had treatment-emergent I38X substitutions. The increased incidence of treatment-emergent resistance in the youngest paediatric subjects observed in study T0835 was also observed in previous studies. In an analysis of pooled datasets, PA I38X baloxavir marboxil treatment-emergent viral resistance mutations were approx. 40% in paediatric subjects < 5 years of age, approx. 15% in those ≥ 5 to < 12 years of age, and approx. 7% in adolescents ≥ 12 years of age and adults. This might be due to a higher viral load as well as a more immature immune system in younger infants. Of note, the same observation has been made for oseltamivir in children, but with significantly lower rates (5-10%) of resistance emergence. In case of treatment-emergent resistance viral mutations, there may be

concerns regarding clinical efficacy and diffusion of baloxavir marboxil-resistant influenza viruses in the community, and this issue was raised with the List of Questions.

With its response, the applicant provided the median time to alleviation of influenza signs and symptoms (TTAS) in patients with and without resistant I38X viruses from 1 to 12 years of age from study CP 40563 and 1 to 5 years of age from pooled datasets of studies CP40563, T0822, T0833, and T0835. This indicated that there was no trend towards patients harbouring resistant viruses having longer TTAS across these age groups. The applicant also provided a literature review with microbiological arguments that resistant variants become the dominant species later in the course of infection, when viral titres are substantially lower than peak viral loads. Indeed, an analysis of the first time of identification of variant sequences from studies CP40559, CP40563, T0822, and T0821 indicated that the majority of variant sequences were first detected on Day 5 or 6. Further, resistance might induce fitness costs for the virus. A published post-hoc analysis of the Phase 3 study T0834 was also provided. It investigated the household transmission of baloxavir marboxil-resistant I38X influenza viruses and suggested a low potential for baloxavir marboxil-resistant influenza virus transmission from treated to untreated individuals. Overall, apart from some case reports there is currently no indication of significant interhuman transmission. However, data are limited because of the recent drug approval and differential use between countries.

Current surveillance data from Japan (NIID), where almost 8 million doses of baloxavir marboxil are estimated to have been administered since approval in February 2018, including more than 1 million doses in paediatric subjects, report only low resistance rates. This is also the case in the USA (CDC), in Europe (ECDC), and according to WHO data. It must nevertheless be taken into account that rates of resistance in routine influenza surveillance programmes are often lower than those of treatment-emergent resistance (such as those observed in a clinical trial) where patients are subjected to the selection pressure of the antiviral treatment.

Post-marketing requirements from the FDA related to resistance consisted of (i) enhanced surveillance with semi-annual baloxavir marboxil resistance reporting and (ii) a Phase 3b surveillance study of susceptibility to baloxavir marboxil (pre-dose and treatment-emergent resistance-associated polymerase acidic protein substitutions) in patients 1 to 12 years of age with influenza (CV44536, Pebblestone). Swissmedic has requested that these results be submitted as post-approval requirements. In addition, Phase 3b clinical trial NCT03969212 (study MV40618) was requested as a post-approval requirement to provide an assessment of the potential for the transmission of resistant variants since this outcome is included as an additional exploratory descriptive endpoint.

5.4 Safety

In addition to safety data evaluated in a previous extension of therapeutic indication application (approved on 19 November 2021; please refer to the relevant SwissPAR), the additional supportive study T0835 was submitted with this application. A total of 45 patients received 1 dose of baloxavir marboxil granules at doses of 14 mg (1 patient, 2.2%), 16 mg (6 patients, 13.3%), 18 mg (2 patients, 4.4%), and 20 mg (36 patients, 80.0%). All patients received the per-protocol assigned amount of study drug except for 2 patients (1 year and 3 years of age) who could not swallow the entire dose of the drug. These patients were still included in the safety population.

Approximately half of the patients (53.3%) had at least 1 AE. The most frequently reported AEs (>5%, that is at least 2 patients) were nasopharyngitis (17.8%), diarrhoea (11.1%), and upper respiratory tract infection (6.7%). All AEs were either Grade 1 (11.1%) or Grade 2 (42.2%) in severity. No severe (Grade ≥ 3) AEs were reported. There were no deaths. Overall, no meaningful differences in the nature and incidence of individual AEs were observed between exposure subgroups.

5.5 Final clinical benefit-risk assessment

Beneficial effects and respective uncertainties

The PK profiles of baloxavir marboxil in the paediatric population were adequately characterised. Overall, similar exposures were observed in paediatric patients as compared to adolescents and adults.

For the treatment indication, in the otherwise healthy 1 to 12 years age group, the effect of baloxavir marboxil in terms of time to alleviation of influenza signs and symptoms was comparable to the active comparator oseltamivir, and the incidence of influenza-related complications was low and similar in both treatment groups. For post-exposure prophylaxis, efficacy was shown in the 1 to 12 years age group. The number of very young patients (1 to 3 years) is limited but PK modelling has shown similar exposure in children down to 1 year of age and it has been accepted that efficacy can be extrapolated from adolescent and adult data.

Unfavourable effects and respective uncertainties

Generally, baloxavir exposures are higher in Asian subjects.

There are no safety concerns specific to the otherwise healthy 1 to 12 years age group. However, there is a significant incidence (approx. 40%) of baloxavir treatment-emergent viral mutations in children under 5 years of age. Current data do not indicate a decrease in treatment efficacy or transmission of baloxavir-resistant influenza viruses. As a result, approval in the 1 to 5 years age group can also be supported, but a specific focus on better understanding of resistance emergence, clinical impact, and potential community spread is warranted. Future surveillance data as well as studies on resistance emergence must be provided to Swissmedic.

Benefit-risk balance

The benefit-risk balance of baloxavir marboxil for treatment of influenza in the otherwise healthy paediatric population 1 to 12 years of age, in the high-risk paediatric population ≥ 12 years of age, and for post-exposure prophylaxis in patients 1 year of age and older is positive.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Xofluza was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Xofluza®

Composition

Active substances

Baloxavirum marboxilum.

Excipients

Tablets
Lactosum monohydricum, carmellosum natricum conexum (produced from genetically modified cotton), povidonum K25, cellulosum microcristallinum, natrii stearylis fumaras, talcum.
Coating: hypromellosum, talcum, titanii dioxidum (E171).
One 20 mg *Xofluza* film-coated tablet contains 77.9 mg lactose monohydrate and 0.6 mg sodium.
One 40 mg *Xofluza* film-coated tablet contains 155.8 mg lactose monohydrate and 1.1 mg sodium.
One 80 mg *Xofluza* film-coated tablet contains 311.6 mg lactose monohydrate and 2.3 mg sodium.

Granules for oral suspension
Mannitolum, maltitolum (E 965), natrii chloridum, hypromellosum, povidonum K25, silica colloidalis anhydrica, sucralosum, talcum and strawberry flavouring.
One bottle of Xofluza contains 700 mg maltitol and 23.59 mg sodium.
1 ml reconstituted suspension contains 1.18 mg sodium and 35 mg maltitol.

Pharmaceutical form and active substance quantity per unit

Xofluza 20 mg film-coated tablets
White to light yellow, oblong film-coated tablets containing 20 mg baloxavir marboxil debossed with "Ⓣ772" on one side and "20" on the other side.
Xofluza 40 mg film-coated tablets
White to light yellow, oblong film-coated tablets containing 40 mg baloxavir marboxil debossed with "BXM40" on one side.
Xofluza 80 mg film-coated tablets
White to light yellow, oblong film-coated tablets containing 80 mg baloxavir marboxil debossed with "BXM80" on one side.

Xofluza 2 mg/ml granules for oral suspension
Xofluza 2 mg/ml granules for oral suspension is white to light yellow and is in a glass bottle. One bottle with 2 g granules for oral suspension contains 40 mg baloxavir marboxil. Following constitution with 20 mL drinking water, the baloxavir marboxil suspension has a final concentration of 2 mg/mL.

Indications/Uses

Treatment of Influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients who have been symptomatic for no more than 48 hours:

- For children aged 1 year and above and adults that are otherwise healthy
  or
- For children aged 12 year and above and adults that are at high risk of developing influenza-related complications

Post-Exposure Prophylaxis of Influenza

Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 1 year and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as no relevant safety and efficacy studies have been conducted to date.

Prescribers should consider available information on influenza virus drug susceptibility patterns and relevant treatment effects (see «*Properties/Effects, Clinical efficacy* and *Resistance monitoring during clinical development*»).

Dosage/Administration

General information

Administer Xofluza using:

• Xofluza tablets or

• Xofluza granules for oral suspension (2 mg/mL).
This formulation is intended for patients or individuals aged 1 to < 12 years, individuals who have difficulty or are unable to swallow tablets, or who require enteral administration. Adults, adolescents and children weighing ≥ 20 kg who are able to swallow tablets may instead receive treatment with Xofluza tablets at a dose of 40 mg or 80 mg depending on the patient’s body weight.

Xofluza may be taken with or without food (see «*Pharmacokinetics*»).

Avoid co-administration of Xofluza with calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium or zinc). Where possible, avoid co-administration of Xofluza with dairy products.

Treatment of Influenza

A single dose of Xofluza should be taken within 48 hours of the onset of symptoms.

Post-exposure Prophylaxis of Influenza

A single dose of Xofluza should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza.

Usual dosage

Treatment or Post-Exposure Prophylaxis of adults, adolescents, children and infants (≥ 1 year of age)

The recommended single oral dose of Xofluza is determined by body weight (see Tables 1 and 2).

Table 1: Xofluza tablets: dosing by patient body weight

Patient body weight (kg)	Recommended single oral dose (tablets)
< 20 kg	refer to table 2 (dosing of Xofluza granules for oral suspension)
≥20 kg to < 80 kg	Single dose of 40 mg taken as 1 x 40 mg tablet OR 2 x 20 mg tablets
≥ 80 kg	Single dose of 80 mg taken as 1 x 80 mg tablet OR 2 x 40 mg tablets

Table 2: Xofluza Granules for Oral Suspension: dosing by patient body weight

Patient Body Weight (kg)	Recommended Single Oral Dose of oral suspension	Volume of oral suspension*
< 20 kg	2 mg per kg of body weight	1 ml per kg of body weight
≥ 20 kg - < 80 kg	40 mg	20 ml
≥ 80 kg	80 mg	40 ml **

* The volume of the suspension in the bottle after reconstitution is 22 mL. The exact volume to be administered should be measured using the oral dispenser(s) included in the carton. e.g., 20 mL of suspension provides the recommended single dose of 40 mg

**Dose requires 2 bottles of Xofluza granules for oral suspension

Dose modifications

No dose reductions are recommended for Xofluza.

Patients with impaired hepatic function

No dose adjustment is required in patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment (see «*Pharmacokinetics, Kinetics in specific patient groups, Hepatic impairment*»). Xofluza has not been studied in patients with severe hepatic impairment.

Patients with impaired renal function

The safety and efficacy of Xofluza has not been studied in patients with renal impairment. No dose adjustment is required in patients with renal impairment (see «*Pharmacokinetics, Kinetics in specific patient groups, Renal impairment*»).

Elderly patients

The safety and efficacy of Xofluza for the treatment of influenza has been studied in geriatric patients aged ≥ 65 years and weighing at least 40 kg (see «*Dosage/Administration, Special dosage instructions, Clinical studies and Pharmacokinetics, Kinetics in specific patient groups*»).
No dose adjustment is recommended.

Children (<12 years of age)

The safety and efficacy in pediatric patients (1 to < 12 years of age) have been established based on the results of two clinical studies (CP40563 and 1719T0834). Safety and efficacy results were consistent with those observed for adults (see «*Pharmacokinetics, Kinetics in specific patient groups, Children and adolescents*»).

The safety and efficacy of Xofluza has not been established in patients aged < 1 year. Xofluza should not be used in these patients.
For patients ≥ 1 year of age see «*Dosage/Administration, Treatment or Post-Exposure Prophylaxis of Children (1 to < 12 years of age)*».

Mode of administration

Tablets
Oral.
Granules for oral suspension
Oral or enteral. For details on preparation and administration of the oral suspension, refer to «*Other information*». The recommended dose can be administered via an enteral feeding tube. The tube should be flushed with water before and after delivering Xofluza. Follow the manufacturer's instructions for the feeding tube to administer the medicine.

Contraindications

Xofluza is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or to any of the excipients. Serious allergic reactions have been observed, including anaphylaxis, angio-oedema, urticarial, and erythema multiforme (see «*Undesirable effects, Undesirable effects after market launch*»).

Warnings and precautions

Cases of anaphylaxis, urticaria, angio-oedema, and erythema multiforme have been reported during post-marketing observation on Xofluza. Appropriate treatment should be carried out if an allergy-like reaction occurs or is suspected (see «*Undesirable effects*»).
Tablets
The tablets contain the excipient lactose monohydrate. Patients with rare hereditary galactose intolerance, complete lactase deficiency or glucose-galactose malabsorption should not use this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is almost "sodium-free".
Granules for oral suspension

The granules contain the excipient maltitol. Patients with rare hereditary fructose intolerance should not use this medicinal product.
This medicinal product contains 23.59 mg sodium (main component in table salt) per bottle. This corresponds to 1.18% of the maximum recommended daily sodium intake in food of 2 g for adults.

Interactions

No clinically significant drug-drug interactions are anticipated between baloxavir marboxil or its active metabolite, baloxavir, and substrates, inhibitors or inducers of cytochrome P450 (CYP enzymes), substrates or inhibitors of UDP-glucuronosyltransferase (UGT) enzyme, or gut, renal, or hepatic transporters.

Pharmacokinetic interactions

Polyvalent cation-containing products may decrease plasma baloxavir concentrations. Xofluza should not be taken concomitantly with polyvalent cation-containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium and magnesium.

Effects of baloxavir marboxil or its active metabolite, baloxavir, on other drugs

Baloxavir marboxil and its active metabolite, baloxavir, did not inhibit any of the following isozymes in the CYP or UGT family in *in vitro* studies conducted at clinically relevant concentrations: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15. Baloxavir marboxil and baloxavir did not cause significant induction of CYP1A2, CYP2B6, and CYP3A4 in *in vitro* studies conducted at clinically relevant concentrations. Baloxavir marboxil and baloxavir inhibited the efflux transporter P-glycoprotein (P-gp) in *in vitro* transporter studies conducted at clinically relevant concentrations. Baloxavir, but not baloxavir marboxil, inhibited BCRP.

Based on *in vitro* transporter studies, despite a weak *in vitro* inhibitory potential, baloxavir is not expected to be an *in vivo* inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K. Therefore, no relevant pharmacokinetic interaction is anticipated between baloxavir and active substances which are substrates of these transporters.

A single 40 mg dose of baloxavir marboxil had no effect on the pharmacokinetics of midazolam, a CYP3A4 substrate. This suggests that neither baloxavir marboxil, nor baloxavir are expected to affect the pharmacokinetics of co-administered drugs that are CYP3A substrates.

A single 80 mg dose of baloxavir marboxil had no effect on the pharmacokinetics of digoxin, a P-gp substrate. This suggests that neither baloxavir marboxil, nor baloxavir are expected to affect the pharmacokinetics of co-administered drugs that are P-gp substrates.

A single 80 mg dose of baloxavir marboxil decreased the C_{max} and $AUC_{0\text{-}inf}$ for rosuvastatin, a BCRP substrate, by 18% and 17%, respectively. These decreases are not considered to be clinically meaningful and indicate that neither baloxavir marboxil, nor baloxavir are expected to affect the pharmacokinetics of co-administered drugs that are BCRP substrates.

Effects of other drugs on baloxavir marboxil or its active metabolite, baloxavir

Itraconazole, a P-gp inhibitor, increased the C_{max} and $AUC_{0\text{-}inf}$ for baloxavir 1.33-fold and 1.23-fold, respectively. These increases are not considered to be clinically meaningful.
Probenecid, a UGT enzyme inhibitor, decreased the C_{max} and $AUC_{0\text{-}inf}$ for baloxavir by 21% and 25%, respectively. These decreases are not considered to be clinically meaningful.

Immune response

No studies have been conducted on the interaction between influenza vaccines and baloxavir marboxil. A clinical study carried out on naturally acquired and experimentally induced influenza revealed that treatment with Xofluza had no adverse effect on the normal humoral antibody response to infection.

Pregnancy, lactation

Pregnancy

No adequate and well-controlled studies have been conducted with Xofluza in pregnant women. The potential risk associated with Xofluza in pregnant women is unknown. Animal experiments have not revealed drug-induced reproductive toxicity (see «*Preclinical data*»). Xofluza should be avoided during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Labour and delivery

The safe use of Xofluza during labour and delivery has not been established.

Lactation

It is not known whether baloxavir marboxil and its active metabolite, baloxavir, are excreted in human milk. Animal experients have shown that baloxavir marboxil passes into maternal milk (see «*Preclinical data*»).
A decision should therefore be made on whether to discontinue nursing and to initiate treatment with Xofluza, taking into consideration the potential benefit of Xofluza to the nursing mother and the potential risk to the infant.

Fertility

No effects were observed on fertility in animal studies conducted with baloxavir marboxil (see «*Preclinical data*»).

Effects on ability to drive and use machines

No studies have been carried out on the effects on the ability to drive and to use machines.

Undesirable effects

The overall safety profile of Xofluza is based on data from 19 clinical studies, in which a total of 2,598 subjects were given Xofluza. Of these, 2272 were adult and adolescent subjects and 326 were pediatric subjects (< 12 years).

Treatment of Influenza

No adverse drug reactions were identified based on pooled data from 3 placebo-controlled clinical studies (studies 1518T0821, 1601T0831 and 1602T0832) carried out in adult and adolescent patients, in which a total of 1640 patients were given Xofluza.
This includes otherwise healthy adults and adolescents, as well as patients at high-risk of developing complications associated with influenza, e.g., elderly patients and patients with chronic cardiac or respiratory disease. 1’334 patients (81.3%) were adults aged ≥ 18 to ≤ 64 years, 209 patients (12.7%) were adults aged ≥ 65 years, and 97 patients (5.9%) were adolescents (aged ≥ 12 to < 18 years). Of these 1’640 patients, 1’440 patients received Xofluza at a dose of 40 mg or 80 mg and 100 patients each received a dose of 10 mg or 20 mg. The safety profile in patients at high-risk was similar to that in otherwise healthy adults and adolescents.
No adverse drug reactions have been identified in children 1 to < 12 years of age who are otherwise healthy based on one active controlled, double-blind study (CP40563), in which a total of 115 patients received the recommended dosage of Xofluza.

Post-Exposure Prophylaxis of Influenza

No adverse drug reactions have been identified based on a placebo-controlled clinical study (study 1719T0834) in 374 subjects, of which 303 were adult and adolescent subjects ≥ 12 years, received Xofluza (see «*Properties/Effects, Clinical efficacy, Post-Exposure Prophylaxis of Infuenza, BLOCKSTONE (Study 1719T0834)*»).

Undesirable effects from the post-marketing phase

The following undesirable effects of baloxavir marboxil were identified after the market launch based on spontaneous case reports and cases from non-interventional study programs. Undesirable effects are listed according to MedDRA system organ classes and the estimated frequency category for each undesirable effect is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1'000 to < 1/100); rare (≥ 1/10'000 to < 1/1'000); very rare (< 1/10'000); not known (cannot be estimated based on the available data).

Immune system disorders
Not known: anaphylaxis [1]
Not known: anaphylactic reactions, including anaphylactic shock [1]
Not known: hypersensitivity [1]
Not known: erythema multiforme

Skin and subcutaneous tissue disorders
Uncommon: urticaria [2]
Not known: angio-oedema [1]

[1] was not observed in the clinical trial. A reliable estimate of their frequency is not possible as these events were reported on a voluntary basis, on a patient collective for which the sample size is not known.
[2] was calculated based on the frequency of events in completed clinical studies.

Description of selected undesirable effects from the post-marketing phase

Hypersensitivity reactions were reported after the market launch, including anaphylaxis/anaphylactic reactions, on the one hand, as well as less serious hypersensitivity reactions, such as urticaria and angio-oedema.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Reports on overdoses with Xofluza originate from clinical trials and postmarketing experience. No adverse events were noted in the majority of cases reporting an overdose. While cases of overdose were reported in association with adverse events, the data are insufficient to determine what symptoms are to be expected as a result of an overdose.

Treatment

There is no known antidote to Xofluza. In the event of an overdose, standard supportive medical care should be initiated based on the patient's signs and symptoms.

Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding.

Properties/Effects

ATC code

J05AX25

Mechanism of action

Baloxavir marboxil is a prodrug that is converted by hydrolysis into its active metabolite, baloxavir, the active form that exerts anti-influenza activity. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex, and thereby inhibits the transcription of influenza virus genomes, resulting in the inhibition of influenza virus replication. The mean inhibitory concentration (IC_{50}) of baloxavir was 1.4 to 3.1 nmol/L for influenza A viruses and 4.5 to 8.9 nmol/L for influenza B viruses in an enzyme inhibition assay.

Pharmacodynamics

Preclinical studies demonstrate potent antiviral activity of baloxavir against influenza A and B virus *in vitro* and *in vivo*. The antiviral activity of baloxavir against laboratory strains and clinical isolates of influenza A and B viruses was determined in the MDCK cell culture assay. The median effective concentration (EC_{50}) of baloxavir was 0.73 nmol/L (n=31; range: 0.20-1.85 nmol/L) for subtype A/H1N1 strains, 0.83 nmol/L (n=33; range: 0.35-2.63 nmol/L) for subtype A/H3N2 strains, and 5.97 nmol/L (n=30; range: 2.67-14.23 nmol/L) for type B strains. In a MDCK cell-based virus titer reduction assay, the EC90 (90% effective concentration) values for baloxavir were in the range of 0.46 to 0.98 nmol/L for subtype A/H1N1 and A/H3N2 viruses, 0.80 to 3.16 nmol/L for avian subtype A/H5N1 and A/H7N9 viruses, and 2.21 to 6.48 nmol/L for type B viruses.

Viruses bearing the PA/I38T/M/F/N/S mutation, selected *in vitro* or in clinical studies, exhibited reduced susceptibility to baloxavir. Baloxavir is effective against neuraminidase inhibitor-resistant strains, including H274Y in A/H1N1, E119V and R292K in A/H3N2, and R152K and D198E in type B viruses, H274Y in A/H5N1, R292K in A/H7N9.

The relationship between antiviral activity in cell culture and inhibition of influenza virus replication in humans has not been investigated.

Xofluza did not prolong the QTc interval at a concentration corresponding to twice the expected exposure compared with recommended dosing.

Clinical efficacy

Treatment of Influenza

Otherwise Healthy Adult and Adolescent Patients

CAPSTONE-1 (Study 1601T0831)

Study 1601T0831 is a randomised, double-blind, multicentre, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo or oseltamivir in otherwise healthy adult and adolescent patients (aged ≥ 12 to ≤ 64 years, weighing at least 40 kg) with influenza.

A total of 1’436 patients were treated in this study in the 2016-2017 Northern Hemisphere influenza season. Patients were randomised to receive 40 mg or 80 mg Xofluza according to their weight (< 80 kg or ≥ 80 kg, respectively), or oseltamivir 75 mg twice daily for 5 days (if aged > 20 years), or placebo. The predominant influenza virus strain in this study was the A/H3 subtype (84.8% to 88.1%), followed by the B type (8.3% to 9.0%) and the A/H1N1pdm subtype (0.5% to 3.0%). In this study, 78% of patients were Asian, 17% were White, and 4% were Black or African American. Out of the 1’436 patients who were enrolled, 1’062 had influenza confirmed by reverse transcription polymerase chain reaction (RT-PCR) and were included in the efficacy analysis (Xofluza n=455, placebo n=230 or oseltamivir n=377). The primary efficacy endpoint was time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue). A statistically significant improvement was seen in the primary endpoint for Xofluza when compared with placebo (see Table 3).

Table 3: Time to Alleviation of Symptoms in Otherwise Healthy Patients with Influenza (Xofluza vs Placebo)

Time to Alleviation of Symptoms (Median [hours])

Xofluza 40/80 mg (95% CI) N=455	Placebo (95% CI) N=230	Difference between Xofluza and placebo (95% CI for difference)	P-value
53.7 (49.5, 58.5)	80.2 (72.6, 87.1)	-26.5 (−35.8, −17.8)	< 0.0001

CI: Confidence interval

There was no statistically significant difference in time to alleviation of symptoms when the Xofluza group was compared with the oseltamivir group (53.5 h vs 53.8 h, respectively). The number of patients who received Xofluza at the recommended dose and who were infected with influenza type B virus was limited to 38 patients. In the influenza B subset, the median time to alleviation of symptoms was 93 hours (95% CI: 53, 135) in patients who received 40 mg or 80 mg Xofluza compared with 77 hours (95% CI: 47, 189) in patients who received placebo.

Study 1518T0821

This phase 2 study was designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo in otherwise healthy adults (aged ≥ 20 to ≤ 64 years) with influenza. A total of 400 patients were randomised to one of three Xofluza dose groups (10, 20 or 40 mg) or placebo in the 2015-2016 influenza season in Japan. The predominant influenza virus strain was the A/H1N1pdm subtype (61% to 71%), followed by the B subtype (21% to 24%) and A/H3N2 subtype (5% to 13%).

The median time to alleviation of symptoms was significantly shorter ($p < 0.05$) in all dose groups compared with the placebo group. Following administration of 40 mg Xofluza, the median time to alleviation of symptoms was 49.5 hours (95% CI: 44.5, 64.4) versus 77.7 hours (95% CI: 67.6, 88.7) in the placebo group.

The number of patients who received Xofluza at the recommended dose and who were infected with influenza type B virus was limited to 24 patients. In the influenza B subset, the median time to alleviation of symptoms was 63 hours (95% CI: 43, 70) in patients who received 40 mg Xofluza compared with 83 hours (95% CI: 58, 93) in subjects who received placebo.

Otherwise Healthy Pediatric Patients (aged 1 to < 12 years)

miniSTONE-2 (Study CP40563)

Study CP40563 was a randomized, double-blind, multicenter, active-controlled study, designed to evaluate the safety, pharmacokinetics and efficacy of a single oral dose of Xofluza compared with oseltamivir in otherwise healthy pediatric patients (aged 1 to < 12 years) with influenza-like symptoms. A total of 173 patients were randomized in a 2:1 ratio to receive a single oral dose of baloxavir marboxil

based on body weight (2 mg/kg for patients weighing < 20 kg or 40 mg for patients weighing ≥ 20 kg) or oseltamivir (dose based on body weight) for 5 days. The predominant influenza virus strain in this study was the A/H3 subtype. The primary objective was to compare the safety of a single dose of baloxavir marboxil with the safety of oseltamivir administered twice daily over 5 days (see section *Undesirable Effects, Treatment of Influenza*). A secondary objective was to compare the efficacy of baloxavir marboxil with oseltamivir based on the efficacy endpoints including time to alleviation of influenza signs and symptoms (cough and nasal symptoms, time to restoration of normal condition in relation to health and activity, as well as duration of fever).

Table 4: Time to Alleviation of Influenza Signs and Symptoms

Time to Alleviation of Symptoms (Median [hours])	
Xofluza (95% CI) N=80	Oseltamivir (95% CI) N=43
138.1 (116.6, 163.2)	150.0 (115.0, 165.7)

Duration of Fever

The median duration of fever was comparable between the Xofluza group (41.2 hours [95% CI: 24.5, 45.7]) and the oseltamivir group (46.8 hours [95% CI: 30.0, 53.5]).

High-Risk Patients

CAPSTONE-2 (Study 1602T0832)

Study 1602T0832 was a randomised, double-blind, multicentre, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo or oseltamivir in adult and adolescent patients (aged ≥ 12 years) with influenza and at high-risk of influenza-related complications (e.g. asthma or chronic lung disease, endocrine disorders, heart disease, age ≥ 65 years, metabolic disorders, morbid obesity).

Patients who had suffered from cancer within the past 5 years (apart from non-melanoma skin cancer), an untreated HIV infection or a treated HIV infection with a CD4 count of below 350 cells/mm^3 in the last 6 months, were not enrolled.

A total of 2’184 patients were randomised to receive a single oral dose of 40 mg or 80 mg Xofluza depending on body weight (40 to < 80 kg or ≥ 80 kg respectively), oseltamivir 75 mg twice daily for 5 days, or placebo. The predominant influenza viruses in this study were the A/H3 subtype (46.9% to 48.8%) and influenza type B (38.3% to 43.5%). Of these patients, 43% were Asian, 46% White and

10% Black or African American (1% other). The majority of patients had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity or were aged 65 or older. In this study, 1'158 of the 2'184 patients who were enrolled had influenza confirmed by RT-PCR and were included in the efficacy analysis (Xofluza n=385, placebo n=385 or oseltamivir n=388). The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue). This endpoint included the alleviation of new symptoms and improvement of any pre-existing symptoms that had deteriorated due to influenza. A statistically significant improvement in the primary endpoint was observed for Xofluza when compared with placebo (see Table 5).

Table 5: Time to Improvement of Influenza Symptoms (Xofluza vs Placebo)

Time to Improvement of Influenza Symptoms (Median [hours])			
Xofluza 40/80 mg (95% CI) N=385	Placebo (95% CI) N=385	Difference between Xofluza and placebo (95% CI for difference)	P-value
73.2 (67.5, 85.1)	102.3 (92.7, 113.1)	-29.1 (−42.8, −14.6)	< 0.0001

When the Xofluza group was compared with the oseltamivir group, there was no statistically significant difference in time to improvement of influenza symptoms (73.2 h vs 81.0 h, respectively).

Virus subtype

For patients infected with the subtype A/H3 virus (predominant strain), the median time to improvement of the symptoms was shorter in the Xofluza group compared with the placebo group, but not compared with the oseltamivir group (see Table 6). In the patients infected with type B virus, the median time to improvement of the symptoms was shorter in the Xofluza group compared with both the placebo and oseltamivir group.

Table 6: Time to Improvement of Symptoms by Influenza Virus Subtype

Time to Improvement of Symptoms (hours) Median [95% CI]			
Virus	Xofluza	Placebo	Oseltamivir

A/H3	75.4 [62.4, 91.6] N=180	100.4 [88.4, 113.4] N=185	68.2 [53.9, 81.0] N=190
B	74.6 [67.4, 90.2] N=166	100.6 [82.8, 115.8] N=167	101.6 [90.5, 114.9] N=148

Incidence of influenza-related complications

There were no significant treatment differences for the complications death, hospitalisation, otitis media and pneumonia.

Post-Exposure Prophylaxis of Influenza

BLOCKSTONE (Study 1719T0834)

Study 1719T0834 was a phase 3, randomized, double-blind, multicenter, placebo-controlled study conducted in 749 subjects in Japan to evaluate the efficacy of a single oral dose of Xofluza compared with placebo in the prevention of influenza in subjects who are household members of influenza-infected patients.

A total of 607 subjects 12 years of age and 142 subjects < 12 years received either baloxavir marboxil dosed according to weight, as in the treatment studies, or placebo. The majority (72.5%) were enrolled within 24 hours of symptom onset in the index patient group. The predominant influenza virus strains in the index patients were the A/H3 subtype (49.1%) and the A/H1N1pdm subtype (47.5%) followed by influenza B (0.7%). The primary efficacy endpoint was the proportion of household subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

Table 7: Proportion of Subjects with Influenza Virus, Fever, and at least one Respiratory Symptom (Xofluza vs Placebo)

Proportion of Subjects with Influenza Virus, Fever, and at least one Respiratory Symptom (%)			
Xofluza (95% CI) N=374	Placebo (95% CI) N=375	Adjusted Risk Ratio (95% CI)	P-value
1.9 (0.8, 3.8)	13.6 (10.3, 17.5)	0.14 (0.06, 0.30)	< 0.0001

Proportion of Subjects ≥ 12 years with Influenza Virus, Fever, and at least one Respiratory Symptom (%)			
N=303 1.3 (0.4, 3.3)	N=304 13.2 (9.6, 17.5)		

Proportion of Subjects <12 years with Influenza Virus, Fever, and at least one Respiratory Symptom (%)*			
N=71 4.2 (0.9, 11.9)	N=71 15.5 (8.0, 26.0)		

* Based on subgroup analysis

Resistance monitoring during clinical development

Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir were detected by the serial passage of the virus in cell culture in the presence of increasing concentrations of baloxavir. Reduced susceptibility of influenza A virus to baloxavir was associated with the amino acid substitutions I38T (H1N1 and H3N2) and E199G (H3N2) in the polymerase acidic (PA) protein of the viral RNA polymerase complex. No influenza B virus isolates with reduced susceptibility to baloxavir were detected in cell culture.

In clinical studies, influenza A virus isolates were detected with treatment-related amino acid substitutions in the PA protein at position I38T/F/M/N/S in association with a > 10-fold reduction in sensitivity to baloxavir and influenza B virus isolates with treatment-related amino acid substitutions in the PA protein at position I38T association with a > 5-fold reduction in sensitivity to baloxavir. The clinical effects of this reduced sensitivity are unclear.

No pre-treatment isolates, with amino acid substitutions associated with a reduced susceptibility to baloxavir, were found in clinical studies. Prescribers should consider available surveillance information (e.g. from WHO or CDC [Centers for Disease Control and Prevention]) on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use Xofluza.

In the phase 3 study conducted in otherwise healthy patients (1601T0831), the amino acid substitution PA/I38T/M was detected in 36 of 370 influenza-infected patients (9.7%) in the Xofluza treatment group. In the phase 3 study conducted in high-risk patients (1602T0832), the amino acid substitution PA/I38T/M/N was detected in 15 of 290 influenza-infected patients (5.2%) in the Xofluza treatment group. In the phase 3 study conducted in paediatric patients (CP40563), the amino acid substitution PA/I38T/M/S was detected in 11 of 57 influenza-infected patients (19.3%) in the Xofluza treatment

group. In the post-exposure prophylaxis study (1719T0834), the amino acid substitution PA/I38T/M was detected in 10 of 374 subjects (2.7%) in the Xofluza group.

Cross-resistance

No single amino acid substitution was identified that might confer cross-resistance between baloxavir and neuraminidase inhibitors (e.g., peramivir, oseltamivir, zanamivir). However, a virus may carry amino acid substitutions in the PA protein and in the neuraminidase that are associated with a reduced susceptibility to baloxavir and to neuraminidase inhibitors, respectively, and which effect reduced susceptibility to both classes of inhibitors. The clinical relevance of evaluations of phenotypic cross-resistance has not been investigated.

Pharmacokinetics

Absorption

After oral administration, baloxavir marboxil is converted into its active metabolite, baloxavir, predominantly by arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and liver. The plasma concentration of baloxavir marboxil was very low or below the limit of quantitation (< 0.100 ng/mL).

The pharmacokinetic parameters for baloxavir in healthy Japanese adults after a single oral administration of 40 mg baloxavir marboxil in the fasting and postprandial states are summarised in Table 8. The pharmacokinetic parameters for baloxavir in healthy Caucasian adults after a single oral administration of 80 mg baloxavir marboxil in the fasting state are summarised in Table 9.

Table 8: Pharmacokinetic Parameters for Baloxavir in the Plasma in Healthy Japanese Adults after Administration of a Single Oral Dose of 40 mg of Baloxavir Marboxil in the Fasting and Postprandial States

Parameters	Geometric Mean (CV%)	
	Fasting	Postprandial
N	14	14
C_{max} (ng/mL)	130 (24.1)	67.6 (40.0)
T_{max}[a] (h)	4.00 (3.00, 5.00)	4.00 (0.50, 5.00)
$AUC_{0\text{-last}}$ (ng·h/mL)	6’932 (19.2)	4’406 (38.8)
$AUC_{0\text{-inf}}$ (ng·h/mL)	7’086 (19.6)	4’540 (39.1)

$t_{1/2,z}$ (h)	93.9 (21.6)	97.5 (22.8)
CL/F (L/h)	4.78 (19.6)	7.45 (39.1)
V_z/F (L)	647 (19.1)	1’050 (35.6)

[a] Median (min, max)

Table 9: Pharmacokinetic Parameters for Baloxavir in the Plasma in Healthy Caucasian Adults after Administration of a Single Oral Dose of 80 mg of Baloxavir Marboxil in the Fasting State (Study 1612T081C)

Parameters	Geometric Mean (CV%)
N	12
C_{max} (ng/mL)	145 (25.4)
$AUC_{0\text{-last}}$ (ng·h/mL)	6’305 (21.2)
$AUC_{0\text{-inf}}$ (ng·h/mL)	6’551 (22.5)
$t_{1/2,z}$ (h)	79.1 (22.4)
CL/F (L/h)	10.3 (22.5)

Following a single oral administration of 80 mg of baloxavir marboxil, the time to peak plasma baloxavir concentration (T_{max}) was reached after approximately 4 hours in the fasting state. The absolute bioavailability of baloxavir marboxil was not investigated.

A food-effect study on absorption, involving the administration of baloxavir marboxil to healthy volunteers under fasting conditions and after a meal (approximately 400 to 500 kcal, including 150 kcal from fat), indicated that the C_{max} and AUC for baloxavir were decreased by 48% and 36%, respectively, after a meal. T_{max} was unchanged in the presence of food. No clinically relevant differences in efficacy were observed in clinical studies with influenza patients where Xofluza was administered with or without food.

Distribution

In an *in vitro* study, the binding of baloxavir to human serum proteins, primarily albumin, was 92.9% to 93.9%. The apparent volume of distribution for baloxavir following a single oral administration of 80 mg of baloxavir marboxil is approximately 1’180 litres in Caucasian patients and 647 litres in Japanese subjects.

Metabolism

In vitro studies revealed that baloxavir marboxil is primarily converted to baloxavir by arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and the liver. Baloxavir is primarily metabolised by UGT1A3, with a minor contribution from CYP3A4.

In a human mass balance study, after administration of a single oral dose of 40 mg of [^{14}C]-labelled baloxavir marboxil, the active metabolite baloxavir accounted for 82.2% of total radioactivity in the plasma. Baloxavir glucuronide (16.4% of total radioactivity in the plasma) and (12aR,5R,11S) sulfoxide of baloxavir (1.5% of total radioactivity in the plasma) were also detected in the plasma. This confirms that the *in vivo* metabolism of baloxavir marboxil occurs via ester hydrolysis to form baloxavir, with subsequent decomposition into sulfoxides and a glucuronide.

Excretion

Baloxavir marboxil and baloxavir were excreted mainly via the faeces in humans. Following a single oral administration of 40 mg of [^{14}C]-labelled baloxavir marboxil, the proportion of total radioactivity eliminated in the faeces was 80.1% of the administered dose, 14.7% was excreted in the urine. The amount of baloxavir excreted in the urine was 3.3% of the administered dose, 48.7% was excreted in the faeces.

Elimination

The apparent terminal elimination half-life ($t_{1/2,z}$) for baloxavir after a single oral administration of baloxavir marboxil is 79.1 hours in Caucasian patients, and 93.9 hours in Japanese subjects, see Tables 8 and 9.

Linearity/non-linearity

Following the single oral administration of 6 mg to 80 mg baloxavir marboxil, baloxavir exhibits linear pharmacokinetics in the fasting state.

Kinetics in specific patient groups

Body weight

Body weight was a significant covariate of the pharmacokinetics of baloxavir based on the population-related pharmacokinetic analysis. The dosage recommendations for baloxavir marboxil are based on body weight both for adults, as well as paediatric patients (see «Dosage/Administration»).

Gender

A population pharmacokinetic analysis did not identify a clinically meaningful effect of gender on the pharmacokinetics of baloxavir. Therefore, no dose adjustment is required based on gender.

Ethnicity

Based on a population pharmacokinetic analysis, ethnicity was identified as a covariate of plasma clearance of baloxavir after oral administration (CL/F), in addition to body weight. However, no dose adjustment is required for baloxavir marboxil based on ethnicity.

Age

A population pharmacokinetic analysis of baloxavir plasma concentrations in patients aged 1 to 64 years who received baloxavir marboxil in clinical studies did not identify age as a clinically relevant covariate for the pharmacokinetics of baloxavir.

Hepatic impairment

Geometric mean values (90% confidence interval) for C_{max} and AUC in patients with moderate hepatic impairment (Child-Pugh class B) compared with healthy controls were 0.80 (0.50 – 1.28) and 1.12 (0.78 – 1.61), respectively. Since no clinically meaningful differences were observed in the pharmacokinetics of baloxavir in patients with moderate hepatic impairment (Child-Pugh class B) compared with healthy controls with normal hepatic function, no dose adjustment is required in patients with mild or moderate hepatic impairment.
The pharmacokinetics have not been investigated in patients with severe hepatic impairment.

Renal impairment

The effects of renal impairment on the pharmacokinetics of baloxavir marboxil or baloxavir have not been investigated. Renal impairment is not expected to alter the elimination of baloxavir marboxil or baloxavir. Renal excretion represents a minor pathway of elimination for baloxavir marboxil or baloxavir. A population pharmacokinetic analysis did not identify a clinically meaningful effect of renal function on the pharmacokinetics of baloxavir. No dose adjustment is required in patients with renal impairment.
Baloxavir is unlikely to be significantly removed by dialysis.

Elderly patients

Pharmacokinetic data collected in patients aged ≥ 65 years show that exposure to the active substance, baloxavir, was similar to that in patients aged ≥ 12 to 64 years.

Children and adolescents

Pharmacokinetic data of baloxavir collected in patients aged 1 to < 12 years show that the body weight-adjusted dosing regimen (2 mg/kg up to 20 kg and 40 mg for ≥ 20 kg) provides similar drug exposures to a 40 mg dose of baloxavir marboxil in adults and adolescents; this also applies to the body weight classes in the paediatric population.

The pharmacokinetics of Xofluza have not been investigated in paediatric patients below 1 year of age.

Preclinical data

Non-clinical data reveal no particular risks to humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity.

Mutagenicity

The pro-drug baloxavir marboxil and its active form, baloxavir, were negative in bacterial reverse mutation tests and in micronucleus tests conducted in mammalian cell cultures. Baloxavir marboxil was negative in an *in vivo* micronucleus test conducted in rodents.

Carcinogenicity

No carcinogenicity studies have been conducted with baloxavir marboxil.

Reproductive toxicity

Baloxavir marboxil had no effects on fertility when administered orally to male and female rats at doses of up to 1’000 mg/kg/day (equivalent to 5 times the human exposure based on $AUC_{0\text{-}24h}$).
Baloxavir marboxil did not cause malformations in rats or rabbits. A study conducted on the embryo-foetal development in rats after the oral administration of daily doses of baloxavir marboxil from gestation day 6 to 17 revealed no signs of maternal or foetal toxicity up to the highest tested dose of 1’000 mg/kg/day (equivalent to 5 times the human exposure based on $AUC_{0\text{-}24h}$).
In rabbits, a dose of 1’000 mg/kg/day (equivalent to 14 times the human exposure based on $AUC_{0\text{-}24h}$) caused maternal toxicity, resulting in 2 miscarriages (out of a total of 19 pregnancies) and an increased number of foetuses with skeletal variation (cervical rib), but no malformations. A dose of 100 mg/kg/day (equivalent to 6 times the human exposure based on $AUC_{0\text{-}24h}$) caused no adverse effects in rabbits.

The pre- and postnatal study conducted in rats revealed no active substance-related adverse findings in dams and pups up to the highest tested dose of 1’000 mg/kg/day (equivalent to 5 times the human exposure based on $AUC_{0\text{-}24h}$).

When dosed at 1 mg/kg, baloxavir marboxil and its metabolites pass into the milk of lactating rats.

Other information

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Tablets

Do not store above 30 °C.

Store in the original packaging.

Keep out of the reach of children.

Granules for oral suspension

Do not store above 25 °C.

Ensure the container is well sealed and store it in the outer carton to protect the contents from moisture.

Keep out of the reach of children.

Oral suspension, following constitution from granules

Xofluza is intended to be taken immediately after the oral suspension is constituted. Storage time should not exceed 2 hours. Storage temperature should not be above 30 °C. See «Other information, Instructions for handling». Discard the suspension if not used within 2 hours of constitution.

Instructions for handling

Granules for oral suspension

Avoid getting Xofluza on your skin. If Xofluza gets on your skin, rinse the area with water.

Preparation of Xofluza Granules for Oral Suspension (2 mg/mL)

It is recommended that Xofluza granules for oral suspension are constituted by the pharmacist. If necessary, the individual or caregiver can also constitute the oral suspension.

If the healthcare professional does not constitute the oral suspension, they should counsel the individual or caregiver on how to constitute the suspension.

1. Constitute Xofluza granules with 20 mL drinking water.
2. Gently swirl the suspension to ensure that the granules are evenly suspended.
3. For oral administration, draw up suspension with a dispenser via the press-in bottle adapter. For enteral administration, draw up suspension with an enteral syringe via a suitable press-in bottle adapter.
4. The constituted suspension should be taken immediately. Discard the suspension if not used within 2 hours after constitution (see «*Other information, Special precautions for storage, Granules for oral suspension, Oral suspension, following constitution from granules*»).

The patient information should be dispensed to the individual or caregiver. The healthcare professional must instruct the person receiving treatment or the caregiver to read the important instructions on use given in the patient information.

The healthcare professional should indicate the volume of oral suspension (2 mg/mL) to withdraw, based on body weight (see Table 2).

Incompatibilities
No incompatibilities between Xofluza and the recommended dispensers and press-in bottle adapter have been observed.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67426, 68068 (Swissmedic).

Packs

Pack of 2 x 20 mg film-coated tablets (single dose) [B]
Pack of 4 x 20 mg film-coated tablets (single dose) [B]
Pack of 1 x 40 mg film-coated tablet (single dose) [B]
Pack of 2 x 40 mg film-coated tablets (single dose) [B]
Pack of 1 x 80 mg film-coated tablet (single dose) [B]

Bottle with granules for oral suspension (2 mg/ml) (single dose). The pack also contains 1 press-in bottle adapter, 1 measuring cup, 1 dispenser of 10 ml (with transparent plunger) and 1 dispenser of 3 ml (with orange plunger).

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

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