

Date: 28 October 2026

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Extension of dose strength

Xofluza

International non-proprietary name: baloxavir marboxil

Pharmaceutical forms: film-coated tablets, granules for oral suspension

Dosage strength(s): film-coated tablets: 20 mg and 40 mg; granules for oral suspension (bottle): 2 mg / ml; granules for oral suspension (sachet): 10 mg, 30 mg and 40 mg

Route(s) of administration: oral use

Marketing authorisation holder: Roche Pharma (Schweiz) AG

Marketing authorisation no.: 68068

Decision and decision date: approved on 5 August 2026

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.....	3
2	Background information on the procedure	4
2.1	Applicant's request(s) and information regarding procedure	4
2.2	Indication and dosage.....	4
2.2.1	Requested indication	4
2.2.2	Approved indication	4
2.2.3	Requested dosage	5
2.2.4	Approved dosage	5
2.3	Regulatory history (milestones)	5
3	Medical context.....	6
4	Quality aspects	7
4.1	Drug substance	7
4.2	Drug product.....	7
4.3	Quality conclusions.....	8
5	Nonclinical aspects	9
6	Clinical aspects	10
6.1	Clinical pharmacology.....	10
6.2	Dose finding and dose recommendation.....	10
6.3	Efficacy.....	10
6.4	Safety	11
6.5	Final clinical benefit risk assessment.....	12
7	Risk management plan summary	13
8	Appendix.....	14

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
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 _{0-24h}	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
PEP	Post-exposure prophylaxis
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Paediatric 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) and information regarding procedure

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.

Extension(s) of the dose strengths

The applicant requested the addition of a new dose strength or modification of an approved one in accordance with Article 24 TPO.

2.2 Indication and dosage

2.2.1 Requested 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 3 weeks and above and adults who are otherwise healthy
or
- For adolescents aged 12 years and above and adults who 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 3 weeks and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as its safety and efficacy have not yet been adequately established for this purpose.

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*»).

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 3 months and above and adults who are otherwise healthy
or
- For adolescents aged 12 years and above and adults who 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 3 months and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as its safety and efficacy have not yet been adequately established for this purpose.

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*»).

2.2.3 Requested dosage

Summary of the requested standard dosage:

The applicant has requested new body weight-based dosage recommendations of <9 kg (2 mg granulate / kg), ≥9 kg to <15 kg (20 mg granulate), ≥15 kg to <20 kg (30 mg granulate), ≥20 kg to <80 kg (40 mg granulate) and ≥80 kg (80 mg granulate).

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 December 2024
Formal objection	16 December 2024
Response to formal objection	13 February 2025
Formal control completed	12 March 2025
List of Questions (LoQ)	5 August 2025
Response to LoQ	3 November 2025
Preliminary decision	6 February 2026
Response to preliminary decision	7 May 2026
Final decision	5 August 2026
Decision	approval

3 Medical context

Influenza is caused by influenza A and influenza B viruses. There are various subtypes of the A viruses, and two lineages of the B viruses: Victoria and Yamagata. Yamagata has been eliminated thanks to the measures taken to combat the Covid-19 pandemic.

Influenza viruses are 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. Children may also experience nausea, vomiting, and diarrhoea, while older adults may not have a high temperature. 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.

Although influenza virus infection is associated with increased rates of hospitalisation in children with other underlying medical conditions, approximately 50 % of children hospitalised with influenza have no underlying condition. Hospitalisation and mortality rates are greatest among those <6 months of age. (Munoz FM. Seasonal influenza in children: Clinical features and diagnosis. In UpToDate, Edwards MS (Ed), Wolters Kluwer- accessed on 15. September 2026.)

In Switzerland, influenza results in approximately 112,000 to 275,000 medical consultations, several thousand cases of hospitalisation 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 through vaccination.

4 Quality aspects

4.1 Drug substance

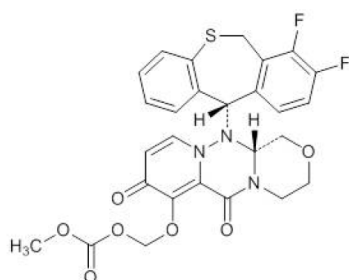
INN: Baloxavir Marboxil

Chemical name: (({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1*H*-[1,4]oxazino[3,4-*c*]pyrido[2,1-*f*][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate

Molecular formula: C₂₇H₂₃F₂N₃O₇S

Molecular mass: 571.55 g/mol

Molecular structure:



Physicochemical properties:

Baloxavir marboxil is a white to light yellow powder. It is practically insoluble in water and is not hygroscopic. The drug substance exhibits polymorphism. The commercial manufacturing process provides Form I.

Synthesis:

Baloxavir marboxil is synthesised in several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps, and intermediates.

Specification:

The drug substance specification includes tests for appearance, identification, assay, related substances, total impurities except S-033447, stereoisomers, residual solvents, water content, residue on ignition, and particle size. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with ICH guidelines.

Stability:

Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition:

Xofluza, granules for preparation of an oral suspension is presented in stickpacks. It is supplied in the four dosage strengths of 10 mg, 30 mg and 40 mg.

Manufacture:

The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data, and including batch manufacturing formula and in-process controls.

Specification:

The drug product specification covers relevant physicochemical characteristics, as well as identification, assay, and purity tests. They allow for proper control of the drug product. The control

methods are validated according to international guidelines. Batch data show consistent quality of the finished product.

Stability:

Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested indication extension. This was considered acceptable. The indication extension will not be associated with a significant risk for the environment.

6 Clinical aspects

6.1 Clinical pharmacology

The Applicant submitted an application for an indication extension for the treatment and post-exposure prophylaxis (PEP) of uncomplicated influenza in otherwise healthy paediatric patients aged 3 weeks to <1 year with influenza symptoms for less than 48 hours.

In addition, the Applicant seeks approval of a new presentation of baloxavir marboxil granules supplied in multiple fixed-dose strengths of stickpacks (sachets), i.e. 10 mg, 30 mg, and 40 mg dose strengths. The new presentation comes with a corresponding weight-based bracket dosing.

The multiple fixed-dose strengths of stickpacks (sachets), i.e. 10 mg, 30 mg, and 40 mg dose strengths, contain granules that are identical to the formulation for granules for oral suspension that is currently approved. The only slight difference is the method of preparation for administration, i.e., for stickpacks the granules are dispersed in a small amount of water. The use of the stickpacks of baloxavir marboxil granules and the corresponding body weight-based dosing was based on population PK model-based simulations allowing for exposure-matching to adults within each race group. Overall, the administration of baloxavir marboxil in stickpack form using the proposed weight bands leads to comparable drug exposures across all body weight ranges, which are also within the adult exposure range.

The pivotal study for the extension of indication is the global phase 3 study CP40559/miniSTONE-1 in otherwise healthy paediatric patients <1 year with influenza-like symptoms. The phase 3 Japanese paediatric studies 1705T0833 and 1813T0835 provide further supportive evidence.

Population PK modelling showed that administration of a 2 mg/kg dose of baloxavir marboxil results in comparable exposure across all age groups <1 year in both non-Asian and Asian paediatric patients as well as in paediatric patients >1 year and in adults.

Positive exposure-response relationships were observed for symptom alleviation (PK-TTAS2 model) and viral kinetics (PK-VK model) using two population PK/PD models.

It should be noted that no new PEP study was conducted.

6.2 Dose finding and dose recommendation

A dedicated dose finding study was not performed in children aged 3 weeks to <1 year with influenza. The proposed body weight-based dosing of the granules (in glass vials or stickpacks) was based on baloxavir marboxil exposure-matching of paediatric patients to adults across all populations.

6.3 Efficacy

Efficacy in patients with influenza aged 3 weeks to <1 year was extrapolated from outcomes in studies in older children, adolescents and adults based on matching baloxavir marboxil exposures. However, this approach is associated with some uncertainty (based on FDA Guidance). Notably, prior exposure to influenza viruses, pre-existing immunity, which may be present in older children, adolescents, and especially in adults, may influence the course of the disease and response to treatment. Furthermore, viral shedding may differ in paediatric and adult age groups.

In addition to the exposure matching approach, data on efficacy (and safety) from the pivotal study CP40559 (miniSTONE-1) were submitted in support of this application.

MiniSTONE-1 was a phase 3, global, multicentre, single-arm study that primarily assessed the safety and pharmacokinetics, and only secondly the efficacy, of a single dose of baloxavir marboxil granules for oral suspension in otherwise healthy paediatric patients in the birth to < 1 year age group with influenza-like symptoms.

Although 49 patients were enrolled, only 15 (30.6%) patients had confirmed influenza and were included in the analysis population for efficacy. Of these, 12 (80.0%) patients aged 3 months to <12

months were in the 2 mg/kg dose group, three (20.0%) patients aged 4 weeks to <3 months were in the 1 mg/kg dose group, and no patients were enrolled in the birth to <1 month age group).

The assessment of the study results was limited by several factors: (1) efficacy was only evaluated as a secondary endpoint without formal statistical analysis, (2) the dosing used in the study was lower than the doses applied for in subjects aged < 3 months, (3) there was no control group, (4) limited number of participants, (5) 20% of the patients had been vaccinated against influenza. Thus, no firm conclusions on efficacy could be drawn from the clinical study results.

Two supportive Japanese, phase 3, multicentre, open-label, single-arm studies (1705T0833 and 1813T0835) assessed the safety, tolerability, PK, and efficacy of a single dose of baloxavir marboxil granules in otherwise healthy Japanese paediatric patients with influenza. In study T0833, six patients aged 43 days to <1 year received a dose of 1 mg/kg baloxavir marboxil, whereas in study T0835, five patients aged 165 days (>3 months) to < 1 year received a dose of 2 mg/kg baloxavir marboxil. As the primary objectives of the studies were descriptive, the sample sizes were limited without a control group, participants were not representative of the Swiss population, and in one study there was a difference between the studied and approved dosing, no firm conclusions on efficacy could be drawn.

The extrapolation of efficacy from older paediatric patients and adults described above was considered acceptable, despite the uncertainties mentioned, as the proposed dosing regimen for children aged 3 weeks to <1 year achieved exposures comparable to those observed in adults. Therefore, no difference in treatment response could be anticipated.

No new study on PEP was conducted.

The efficacy of PEP in infants aged <1 year was extrapolated from older children and adults in phase 3 study T0834, which was conducted entirely in Japan, to collect PK and PD data in paediatric Japanese patients and support the indication extension for the treatment of paediatric patients of 1 to <12 years of age.

The extrapolation of the efficacy results to paediatric patients <1 year regardless of race was based on three steps: (1) In a previous exposure-response analysis, no relationship between baloxavir plasma exposures and PEP failure was observed in subjects aged ≥ 12 years and subjects aged ≤ 12 years. (2) Previous analyses of adults and adolescents showed that baloxavir PK profiles were comparable between otherwise healthy and high-risk adult patients with influenza virus infection and healthy adults. (3) The simulations described for the treatment demonstrated that the 2mg/kg baloxavir marboxil dose ensures comparable exposures over a period of about 240 hours.

As influenza viral shedding usually occurs at or just before the onset of symptoms (0 to 24 hours), peaks at 24 to 48 hours of illness, and then rapidly declines, with little or no detectable virus after five to ten days (Munoz FM. Seasonal influenza in children: Clinical features and diagnosis. In UpToDate, Edwards MS (Ed), Wolters Kluwer- accessed on 15. September 2026.), and can therefore last up to ten days, a period of ten days with sufficient exposures of baloxavir seems adequate.

6.4 Safety

In the pivotal miniSTONE-1 study in patients aged <1 year, diarrhoea and vomiting were the most frequently reported adverse events across both dosing groups.

Diarrhoea, vomiting, and rash were newly identified adverse drug reactions (ADRs) in the clinical trials and have been added to the Information for Healthcare Professionals.

ADRs that were already known from post marketing experience and are listed in the approved Information for healthcare professionals for patients ≥ 1 year are anaphylactic reactions including anaphylactic shock, hypersensitivity reactions, erythema multiforme, urticaria, and angioedema.

No evidence of a clinically relevant safety risk has been identified on the basis of safety data available in patients aged <1 year.

However, given the limited clinical experience in this age group, uncertainty remains. Clinical safety data are particularly limited for infants aged 3 weeks to <3 months, and the assessment is further

complicated by the fact that these infants were exposed to 50% of the proposed dose. Furthermore, due to the organ immaturity of this age group, it is not possible to reliably assess safety based on comparable exposure in older populations.

As the doses for influenza PEP in the proposed age group are identical to those for influenza treatment, the same safety conclusions are applicable.

6.5 Final clinical benefit risk assessment

The proposed dosing regimens for granules (in glass vials or stickpacks), which were based on a baloxavir marboxil exposure-matching approach could be accepted. It is expected that efficacy in children aged 3 months to 1 year is comparable to the already approved efficacy in patients aged ≥ 1 year for treatment or PEP of influenza.

The *available* safety data for the doses administered in the clinical studies were considered acceptable.

Clinical safety data at the proposed dose were not available for patients aged 3 weeks to <3 months as these patients received only 50% of the proposed dose in the clinical study. Given the immaturity of organ function in this age group, safety cannot be reliably assessed based solely on exposure comparability with older populations, and no dose recommendations could be defined.

Accordingly, the benefit-risk ratio for the treatment and post-exposure prophylaxis of influenza is positive for infants aged 3 months to <1 year. The limited safety data in infants aged 3 weeks to <3 months did not allow a benefit-risk assessment in this age group. The available data are presented in the respective sections (safety, efficacy, pharmacokinetics) of the Information for healthcare professionals.

7 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.

8 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-pro.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.

Xofluza®

Composition

Active substances

Baloxavirum marboxilum

Excipients

Tablets

Lactosum monohydricum, carmellosum natricum conexum, povidonum K25, cellulosum microcristallinum, natrii stearyl fumaras, talcum.

Coating: hypromellose, 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 (bottle)

Mannitolum, maltitolum (E 965), natrii chloridum, hypromellose, 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.

Granules for oral suspension (sachet)

Mannitolum, maltitolum (E 965), natrii chloridum, hypromellose, povidonum K25, silica colloidalis anhydrica, sucralosum, talcum and strawberry flavouring.

Xofluza 10 mg granules for oral suspension (sachet)

One sachet of Xofluza contains 175 mg maltitol and 5.9 mg sodium.

Xofluza 30 mg granules for oral suspension (sachet)

One sachet of Xofluza contains 525 mg maltitol and 17.7 mg sodium.

Xofluza 40 mg granules for oral suspension (sachet)

One sachet of Xofluza contains 700 mg maltitol and 23.6 mg sodium.

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 (bottle)

Xofluza 2 mg/ml granules for oral suspension (bottle) are white to light yellow and are 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.

Xofluza 10 mg granules for oral suspension (sachet)

Each sachet contains 500 mg of granules equivalent to 10 mg of baloxavir marboxil. The granules are white to light yellow.

Xofluza 30 mg granules for oral suspension (sachet)

Each sachet contains 1500 mg of granules equivalent to 30 mg of baloxavir marboxil. The granules are white to light yellow.

Xofluza 40 mg granules for oral suspension (sachet)

Each sachet contains 2000 mg of granules equivalent to 40 mg of baloxavir marboxil. The granules are white to light yellow.

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 3 months and above and adults who are otherwise healthy
or
- For adolescents aged 12 years and above and adults who 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 3 months and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as its safety and efficacy have not yet been adequately established for this purpose.

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 (bottle - 2 mg/mL) or
- Xofluza granules for oral suspension (sachet - taken with water).

Individuals who have difficulty or are unable to swallow tablets, or who require enteral administration can use granules for oral suspension (bottle) or granules for oral suspension (sachet) (see Tables 2 and 3). 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 Patients aged 3 months and above

Xofluza can be administered as tablets or granules for oral suspension (bottle) or granules for oral suspension (sachet).

The recommended single oral dose of Xofluza is determined by body weight (see Tables 1,2 and 3).

As an alternative to Xofluza granules for oral suspension (bottle) or Xofluza granules for oral suspension (sachet), children weighing ≥ 20 kg who are able to swallow tablets may instead receive treatment with Xofluza tablets (see Table 1).

Table 1: Xofluza Tablets: Dosing by patient body Weight

Patient body weight (kg)	Recommended single oral dose (tablets)
< 20 kg	Refer to table 2 or 3 (dosing of Xofluza granules for oral suspension (bottle) or Xofluza granules for oral suspension (sachet))
≥ 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 (Bottle): 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 ^b	40 mg	20 mL
≥ 80 kg ^b	80 mg ^a	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.

^a Dose requires 2 bottles of Xofluza Granules for Oral Suspension.

^b Refer also to Xofluza Tablets in Table 1, for patients who are able to swallow the tablet formulation.

Table 3: Xofluza Granules for Oral Suspension (Sachet - taken with water): Dosing by Weight

Patient Body Weight (kg)	Recommended Single Oral Weight-based Bracket ^a Dose
< 9 kg	2 mg/kg ^b
≥ 9 kg to <15 kg	20 mg ^c
≥15 kg to <20 kg	30 mg
≥ 20 kg to < 80 kg ^e	40 mg
≥80 kg ^e	80 mg ^d

^a Weight-based bracket dosing applies to body weight ≥ 9 kg. Body weight < 9 kg follows the weight-based mg/kg dosing (see Table 2).

^b Preparation and administration of a suspension (2 mg/mL) from the granules in the sachet must be done by the healthcare professional. A 2 mg/kg dose requires the 40 mg sachet. See also section "Mode of administration". 1 mL per kg (of body weight) of the suspension must be administered, e.g. a child weighing 8 kg must receive 8 mL of the suspension.

^c Dose requires 2x 10 mg granules in sachet.

^d Dose requires 2x 40 mg granules in sachet.

^e Refer also to Xofluza Tablets in Table 1, for patients who are able to swallow the tablet formulation.

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 use of Xofluza in children aged 3 months and above and under 1 year is based on reaching similar exposures to those that have proven effective in adults and older children and is further supported by the results of a pediatric study in infants (see sections "*Pharmacokinetics*" and "*Properties/Effects*").

There are only limited data on the use of Xofluza in infants aged under 3 months and no dosage recommendation can be made. The data that are currently available are described in the sections "*Properties/Effects*" and "*Pharmacokinetics*".

Mode of administration

Tablets

Oral.

Granules for oral suspension (bottle) and granules for oral suspension (sachet)

Oral or enteral. For details on preparation and administration of the granules for oral suspension (bottle) and for granules for oral suspension (sachet), 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, urticaria, 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».

Xofluza granules for oral suspension (bottle)

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 of sodium per bottle, corresponding to 1.18% of the maximum daily sodium intake of 2 g recommended by the WHO for an adult.

Xofluza granules for oral suspension (sachet)

The granules contain the excipient maltitol. Patients with rare hereditary fructose intolerance should not use this medicinal product.

The 10 mg and 30 mg granules in sachet contain less than 23 mg of sodium per sachet, that is to say essentially 'sodium-free'.

The 40 mg granules in sachet contain 23.59 mg of sodium per sachet, corresponding to 1.18% of the maximum daily sodium intake of 2 g recommended by the WHO for an adult.

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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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 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 experiments 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 21 clinical studies, in which a total of 3'369 subjects were given Xofluza. Of these, 2'929 were adult and adolescent subjects and 440 were pediatric subjects (< 12 years).

Adults and adolescents aged > 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.

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 Influenza, BLOCKSTONE (Study 1719T0834)*»).

Post-marketing Experience

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1'000$ to $< 1/100$); rare ($\geq 1/10'000$ to $< 1/1'000$); very rare ($< 1/10'000$); not known (cannot be estimated based on the available data).

Table 4: Adverse drug reactions from postmarketing experience in adults, adolescents aged > 12 years

System organ class (SOC)	Adverse reaction (preferred term (PT), MedDRA)	Frequency
Immune system disorders	Anaphylaxis ¹	Not known
	Anaphylactic reactions, including anaphylactic shock ¹	Not known
	Hypersensitivity ¹	Not known
	Erythema multiforme	Not known
Gastrointestinal disorders	Diarrhoea ¹	Not known
	Vomiting ¹	Not known
	Colitis ¹	Not known
	Ischaemic colitis ¹	Not known
Skin and subcutaneous disorders	Urticaria ²	Uncommon
	Angioedema ¹	Not known

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.

Children aged < 12 years

The safety profile of baloxavir marboxil in paediatric patients (3 weeks to < 12 years) was determined from data collected from treatment and post exposure prophylaxis studies of one active controlled, double-blind study (CP40563) and one single arm open-label study (CP40559), in which a total of 163 patients received Xofluza. Table 5 presents adverse drug reactions identified from clinical trial and during post-marketing phase experience.

Table 5 Adverse drug reactions in children aged < 12 years

System organ class (SOC)	Adverse reaction (preferred term (PT), MedDRA)	Frequency
Immune system disorders	Anaphylaxis ¹	Not known
	Anaphylactic reactions ¹	Not known
Gastrointestinal disorders	Diarrhoea ²	Common
	Vomiting ²	Common
	Colitis ¹	Not known
	Ischaemic colitis ¹	Not known
Skin and subcutaneous disorders	Rash ²	Common
	Urticaria ¹	Not known
	Angioedema ¹	Not known

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.

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 EIViS 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 (IC₅₀) 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 (EC₅₀) 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 a PA/I38T/M/F/N/S mutation or the PA/T20K 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, 1'057 had influenza confirmed by reverse transcription polymerase chain reaction (RT-PCR) and were included in the efficacy analysis (Xofluza $n=454$, placebo $n=227$ or oseltamivir $n=376$). 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 6).

Table 6: 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=454	Placebo (95% CI) N=227	Difference between Xofluza and placebo (95% CI for difference)	P-value

53.7 (49.5, 57.5)	80.6 (72.6, 88.6)	-26.8 (-35.7, -18.9)	< 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 53.9 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 93.0 hours (95% CI: 53.4, 135.4) in patients who received 40 mg or 80 mg Xofluza compared with 77.1 hours (95% CI: 46.8, 189.0) 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 7: 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]).

Otherwise Healthy Pediatric Patients (aged < 1 year)

Study CP40559

Study CP40559 was a multicenter, single-arm, open-label uncontrolled, unblinded study to evaluate the safety, pharmacokinetics and efficacy of a single oral dose of Xofluza granules in otherwise healthy pediatric patients aged < 1 year with influenza-like symptoms. The youngest patient recruited was about 3 weeks of age.

A total of 48 patients received a single oral dose of baloxavir marboxil based on body weight and age (2 mg/kg for patients ≥ 3 months, 1 mg/kg for patients < 3 months). The predominant influenza virus strain in this study was the A/H3 subtype. The primary objective was to evaluate the safety of a single dose of baloxavir marboxil (see «Undesirable effects»). A secondary objective was to evaluate the efficacy of baloxavir marboxil based on the efficacy endpoints including time to alleviation of influenza signs and symptoms (cough and nasal symptoms, time to return to normal health and activity and duration of fever). The efficacy endpoints were evaluated in the Intent-to-Treat-Infected (ITTi) population. The ITTi population included all patients who received any portion of a single dose and had a laboratory-confirmed influenza infection (RT-PCR) from any swab sample at baseline or during the study. Overall, 15 patients were in the ITTi population with 12 (80%) aged 3 to 12 months and 3 (20%) aged 4 weeks to 3 months.

The median time to alleviation of influenza signs and symptoms was 163.7 hours (N=15, 95% CI 122.5, NE (not evaluable)).

Duration of Fever

The median duration of fever was 23.1 hours (95% CI: 22.3, 44.6, N=13).

Antiviral Activity

Patients treated with Xofluza showed a rapid reduction in virus titer. The median time to cessation of viral shedding determined by virus titer was 24.5 hours (95% CI: 24.2, 68.6, N=10).

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/mm³ 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, 1'145 of the 2'184 patients who were enrolled had influenza confirmed by RT-PCR and were included in the efficacy analysis (Xofluza n=380, placebo n=381 or oseltamivir n=384). 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 8).

Table 8: Time to Improvement of Influenza Symptoms (Xofluza vs Placebo)

Time to Improvement of Influenza Symptoms (Median [hours])			
Xofluza 40/80 mg (95% CI) N=380	Placebo (95% CI) N=381	Difference between Xofluza and placebo (95% CI for difference)	P-value
73.2 (67.2, 85.1)	102.3 (92.7, 113.1)	-29.1 (- 42.4, - 14.7)	< 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 82.2 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 9). 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 9: Time to Improvement of Symptoms by Influenza Virus Subtype

Time to Improvement of Symptoms (hours) Median [95% CI]			
Virus	Xofluza	Placebo	Oseltamivir
A/H3	73.7 [62.4, 90.9] N=176	100.4 [88.4, 113.4] N=185	68.9 [54.0, 81.2] N=188
B	74.6 [67.9, 90.2] N=165	100.6 [82.8, 115.8] N=163	103.7 [90.9, 115.4] N=146

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 over 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 10: 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.

Influenza A virus isolates with treatment-emergent amino acid substitutions I38T/F/M/N/S in the PA protein associated with > 10-fold reduced susceptibility to baloxavir and influenza B virus isolates with treatment-related amino acid substitutions I38T or T20K in the PA protein associated with > 5-fold reduced susceptibility to baloxavir were observed in clinical studies. The clinical impact of this reduced susceptibility is 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 in pediatric patients aged 1 to <12 years (CP40563), PA/I38T/M/S were detected in 11 of 57 influenza-infected patients (19.3%) in the Xofluza treatment group. In the phase 3 study in pediatric patients aged <1 year (CP40559), PA/I38T and PA/T20K were detected in 2 of 13 (15.4%) influenza-infected subjects treated with Xofluza. 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).

Pharmacokinetic (PK) parameters of baloxavir have been characterised in healthy adult subjects and in patients with influenza-like symptoms. Baloxavir's PK was best described by a population PK model with a two-compartment disposition model with first-order absorption and elimination processes, including a sigmoid E_{max} model to quantify the clearance maturation with age in toddlers. Body weight and race were found to have a significant effects on the PK.

In adults, after single administration of baloxavir marboxil at the therapeutic dose of 40 mg for adult patients < 80 kg, and of 80 mg for adult patients ≥ 80 kg, the estimated mean baloxavir AUC_{0-inf} were 9'580 and 4'750 ng.hr/mL, and the estimated mean C_{max} were 95.2 and 62.4 ng/mL in the Asian and non-Asian populations, respectively.

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. The absolute bioavailability of baloxavir marboxil was not investigated.

In a food-effect study after administration of baloxavir marboxil at a 40 mg dose to healthy volunteers, C_{max} and AUC_{0-inf} of baloxavir were decreased by 48% (geometric mean (CV%) of 67.6 (40.0) vs 130 (24.1) ng/mL) and 36% (geometric mean (SD) of 4'540 (38.8) vs 7'090 (19.6) ng.hr/mL), when given in fed conditions (with a meal of approximately 400 to 500 kcal including 150 kcal from fat) compared to fasting conditions, respectively. 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 determined by non-compartmental analysis 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. The population PK parameter estimates were 260 L for the apparent peripheral volume, and 489 L and 735 L for the apparent central volume of distribution in the Asian and non-Asian populations, respectively.

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 [¹⁴C]-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 [¹⁴C]-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% of the administered dose, and the amount of baloxavir excreted in the feces was 48.7% of the administered dose.

Elimination

Population PK analyses estimated an apparent clearance (CL/F) of 5.47 and 11.02 L/h for baloxavir in the Asian and non-Asian populations, respectively.

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. Based on the population pharmacokinetic analysis, baloxavir apparent oral clearance (CL/F) and apparent volume of distribution for central compartment (V_c/F) increased with body weight with different exponents, therefore half-life is shorter in patients with a lower body weight (i.e., a shorter $t_{1/2}$ in pediatric patients when compared to adults) (see Table 11). See «Pharmacokinetics, Ethnicity».

Table 11: Baloxavir half-life per age and race

	< 12 years of age		≥ 12 years of age	
	Non-Asians	Asians	Non-Asians	Asians
t_{1/2} (h) Mean (SD)	29.4 (9.9)	35.6 (8.17)	50.3 (12.6)	59.6 (13.5)

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 age-independent covariate based on the population pharmacokinetic analysis. Therefore, dosing was adjusted according to body weight in both adult and paediatric individuals (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 and V_d/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 85 years who received baloxavir marboxil in clinical studies did not identify age as a clinically relevant covariate for the pharmacokinetics of baloxavir. In a population PK analysis including 57 pediatric patients under 1 year of age, age significantly influenced baloxavir CL/F; a maturation half-life of 38.3 weeks was estimated. No dose adjustment of baloxavir marboxil based on age is required.

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 were collected in patients aged 3 weeks to < 12 years. The body weight-adjusted dosing regimen (2 mg/kg up to 20 kg and 40 mg for ≥ 20 kg) provides similar drug exposures to the therapeutic body weight-adjusted doses of baloxavir marboxil in adults (40 mg for adult patients < 80 kg, and of 80 mg for adult patients ≥ 80 kg) in both Asian and non-Asian populations (see Table 12).

Table 12: Mean (5th – 95th percentile) pharmacokinetic parameters of baloxavir in non-Asian patients aged 3 weeks and above receiving a single oral baloxavir marboxil administration

Age group	Dose group*	N	AUC _{0-inf} (ng.hr/mL)	C _{max} (ng/mL)	C ₇₂ (ng/mL)	T _{max} (hr)	T _{1/2} (hr)
22 - < 28 days	1 mg/kg**	1	2640 [NA,NA]***	66.9 [NA,NA]	8.71 [NA,NA]	5 [NA,NA]	23.4 [NA,NA]

Age group	Dose group*	N	AUC _{0-inf} (ng.hr/mL)	C _{max} (ng/mL)	C ₇₂ (ng/mL)	T _{max} (hr)	T _{1/2} (hr)
28 days - <3 months	1 mg/kg**	8	2580 [864,4880]	57.1 [37.1,80.4]	9.53 [1.3,20.3]	6.5 [2,13]	25.2 [13,32.8]
3 months - < 1 year	2 mg/kg	37	5670 [1800,11900]	144 [48.8,294]	18.4 [4.43,41.5]	5.09 [2,13]	22.9 [15.5,30.3]
1 - < 2 years	2 mg/kg	8	3260 [1670,5970]	95.5 [33.1,215]	10.0 [2.02,14.2]	3.56 [1.5,7]	23 [11.6,38.8]
2 - < 12 years	2 mg/kg	32	4490 [765,9070]	116 [21.4,272]	15.0 [3.06,32.2]	3.94 [1.5,7.5]	24.2 [17.4,35.3]
	40 mg	64	4650 [1770,9130]	87.1 [31.1,147]	19.1 [7.36,39.2]	5.51 [2.5,10.5]	33.8 [21.7,52.4]
12 - < 18 years	40 mg	44	3520 [1230,7470]	52.7 [17.5,94.3]	15.5 [5.76,31.2]	4.32 [1.5,7.5]	42.9 [32,69]
	80 mg	13	6600 [2730,11600]	83.7 [43.9,147]	29.6 [12.1,51.7]	5.19 [1,13]	50.7 [34.2,64.5]
18 years and above	40 mg	310	3470 [1440,6350]	47.4 [20.6,86.2]	15.4 [6.36,27.8]	4.67 [1.5,10]	47.7 [31.2,67.5]
	80 mg	338	5880 [2270,11200]	73.4 [27.5,141]	26.2 [10.7,49.4]	5.19 [2,11]	52.8 [33.6,76.2]

* Dose groups are based on bodyweight: < 20 kg: 2 mg/kg; ≥ 20 kg - < 80 kg: 40 mg; ≥ 80 kg: 80 mg;

** For age categories with no PK observations at the recommended dose of baloxavir marboxil, population-PK modeling predicts that a dose of 2 mg/kg in children 22 days to 3 months of age produces a similar exposure as adults and older children.

*** NA: not available

The pharmacokinetics of baloxavir have not been established in paediatric patients below 3 weeks 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_{0-24h}).

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_{0-24h}).

In rabbits, a dose of 1'000 mg/kg/day (equivalent to 14 times the human exposure based on AUC_{0-24h}) caused maternal toxicity, resulting in 2 miscarriages (out of a total of 19 pregnancies) and an increased number of fetuses 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_{0-24h}) 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_{0-24h}).

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(bottle)

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.

Granules for oral suspension (sachet)

Do not store above 30°C.

Keep out of the reach of children.

Oral suspension, following constitution from Xofluza granules for oral suspension (bottle) or Xofluza 40 mg granules for oral suspension (sachet - for patients weighing < 9 kg)

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.

For patients weighing ≥ 9 kg Xofluza granules for oral suspension (sachet) should be taken / given immediately after mixing with water.

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) [B]

Pack of 2 x 10 mg sachets (single dose) [B]

Pack of 1 x 30 mg sachets (single dose) [B]

Pack of 1 x 40 mg sachets (single dose) [B]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

Date of revision of the text

July 2026.

Instructions for handling

For administration via an enteral feeding tube, the tube should be flushed with water before and after delivering Xofluzo. Follow the manufacturer's instructions for the feeding tube to administer the medicine.

Granules for oral suspension (bottle)

Avoid getting Xofluzo (and the liquid after mixing) on your skin. If Xofluzo gets on your skin, rinse the area with water.

Preparation of Xofluzo Granules for Oral Suspension (bottle - 2 mg/mL)

It is recommended that Xofluzo granules for oral suspension are constituted by a healthcare professional. If necessary, the individual or caregiver can also constitute the oral suspension. If the healthcare professional does not constitute the oral suspension, they must counsel the individual or caregiver on how to constitute the suspension.

1. Constitute Xofluzo granules for oral suspension with 20 mL drinking water.
2. Gently swirl the suspension to ensure that the granules are evenly suspended.
3. Do not shake the bottle.

4. For oral administration, draw up suspension with a dispenser via a suitable press-in bottle adapter. For enteral administration, draw up suspension with an enteral syringe via a suitable press-in bottle adapter.
5. 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 Xofluza granules for oral suspension (bottle) or Xofluza 40 mg granules for oral suspension (sachet - for patients weighing < 9 kg)*»).

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.

Granules for oral suspension (sachet)

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

Xofluza granules should be taken immediately after mixing with water.

Preparation of Xofluza granules in sachet 10 mg, 30 mg and 40 mg

For Patients who weigh < 9 kg

Preparation and administration of the suspension (2mg/mL) must be done by the healthcare professional.

For preparation and administration, the use of a glass bottle (e.g. 50 mL), suitable press-in bottle adapter and oral syringe is preferred.

1. For the 2 mg/kg dose, use only the 40 mg granules in sachet.
2. Tap the sachet to ensure the granules are on one side of the sachet.
3. Open the sachet and add the granules into the bottle. Tap the sachet to ensure all the granules have been removed.
4. Constitute the granules with a measured 18.5 mL of drinking water.
5. Do not shake the bottle.
6. Gently swirl the suspension to ensure that the granules are evenly suspended.

7. Measure the correct volume of suspension using an oral syringe (oral administration) or enteral syringe (enteral administration) and administer immediately. 1 mL per kg (of body weight) of the suspension must be administered, e.g. a child weighing 8 kg should receive 8 mL of the suspension. Discard the suspension if not used within 2 hours after constitution (see «Other information, Special precautions for storage, Oral suspension, following constitution from Xofluza granules for oral suspension or Xofluza 40 mg granules in sachet (for patients weighing < 9 kg)»).

Once the suspension is prepared for administration and the correct volume administered, it cannot be used again. The remaining suspension must be discarded and disposed of in accordance with local requirements.

For Patients who weigh ≥ 9 kg:

Preparation and administration to be done by the individual or care giver

1. Tap the sachet to ensure the granules are on one side of the sachet. Two sachets may be required depending on the dose (see Table 3).
 - 1a. For a 20 mg dose, use two 10 mg sachets as instructed below. Take the sachets together.
 - 1b. For an 80 mg dose, use two 40 mg sachets. Take the sachets separately. Follow steps 2-8 to take the first sachet then repeat steps 2-8 to take the second sachet.
2. Open the sachet(s) and add the granules into a small cup containing a small amount of drinking water (i.e. 1 tablespoon, approximately 15-20 mL).
3. Tap the sachet(s) to ensure all granules have been removed.
4. Gently swirl the cup for 1 minute or until the granules have fully dispersed.
5. Drink immediately.
6. Refill the cup with approximately 15-20 mL of drinking water and swirl to get any remaining granules.
7. Drink immediately.
8. Repeat steps 6 and 7 one more time if there are still remaining granules in the cup.