Date: 8 May 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Xofluza

International non-proprietary name: baloxavir marboxil
Pharmaceutical form: film-coated tablets
Dosage strength: 20 mg, 40 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 67426
Decision and Decision date: approved on 19 February 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CEN	Cap-dependent endonuclease
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
EC_{90}	Effective concentration for 90% inhibition
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MDCK	Madin-Darby canine kidney
Min	Minimum
NA	Neuraminidase
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PA	Polymerase acidic protein
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
T_{max}	Time to reach the maximum concentration
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)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a worksharing procedure with Australia, Canada and Switzerland.
The ACSS NAS (New Active Substances) work sharing initiative is a collaboration between regulatory authorities Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA) and Swissmedic and the pharmaceutical industry.
The work sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

For aspects of the evaluation not covered in this SwissPAR, please refer to the publicly available assessment reports for Xofluza issued by the regulatory authorities HC and TGA (see https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html and https://www.tga.gov.au/ws-auspar-index)

2.2 Indication and Dosage

2.2.1 Requested Indication

XOFLUZA is indicated for the treatment of influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours (see section Properties/Effects, Clinical Efficacy).
XOFLUZA is indicated for the treatment of influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours and who are at high risk of developing influenza-related complications (see section *Properties/Effects, Clinical efficacy*).

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

2.2.2 Approved Indication

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours and who are:
• otherwise healthy, or
• at high risk of developing influenza-related complications.

Limitations of use
Baloxavir is not indicated for use as prophylaxis against influenza during a flu epidemic 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 sections *Properties/Effects, Clinical efficacy* and *Resistance monitoring during clinical development*).

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2.2.3 Requested Dosage

- A single dose of XOFLUZA should be taken within 48 hours of symptom onset. XOFLUZA can be taken with or without food (see section Pharmacokinetics).
- Adults and children ≥ 12 years of age:
  - The recommended dose for patients with a body weight of 40 kg to less than 80 kg is a single dose of 40 mg
  - The recommended dose for patients with a body weight of at least 80 kg is a single dose of 80 mg

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	30 April 2019
Formal control completed	7 May 2019
List of Questions (LoQ)	27 September 2019
Answers to LoQ	28 October 2019
Predecision	20 December 2019
Answers to Predecision	17 January 2020
Final Decision	19 February 2020
Decision	approval

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1. Applicant's request/Work-sharing procedure).

4 Nonclinical Aspects

The applicant provided a comprehensive study package on Xofluza (baloxavir marboxil), a prodrug hydrolysed to the active compound baloxavir. This is the *"first-in-class"* compound that inhibits the cap-dependent endonuclease (CEN) activity of the influenza virus PA (polymerase acidic protein) polymerase complex. Pivotal safety pharmacology and toxicology studies were conducted in compliance with good laboratory practice (GLP).

Pharmacodynamic

Baloxavir inhibited the transcription of virus A and B strains by inhibition of CEN activity, with a higher potency against virus A strains than B strains (IC_{50} 1.4-3.1 nM and 4.5-8.9 nM, respectively). *In vitro* antiviral assays (endpoints: virus titre reduction, plaque reduction, or cytopathic effect) were mainly performed using Madin-Darby canine kidney (MDCK) cells infected with a broad spectrum of viruses (laboratory strains, seasonal influenza viruses, and clinical isolates). In a virus titre reduction assay, baloxavir was more efficient in inhibiting virus replication in highly virulent A strains (EC_{90} 0.46-0.98 nM in A/H1N1 and A/H3N2) than in B strains (EC_{90} range: 2.21-6.48 nM). Similar results were obtained in a cellular-based plaque formation inhibition assay, where EC_{50} values ranged from 0.20-1.85 nM for subtype A/H1N1 strains, 0.35-2.63 nM for subtype A/H3N2 strains, and 2.67-4.23 nM for type B strains. Baloxavir also showed antiviral activity against avian strains (H5N1, H7N9) and NA (neuraminidase) inhibitor-resistant strains carrying different mutations in NA protein.
Baloxavir showed superior efficacy against laboratory strains compared to other approved antiviral agents. Combination of baloxavir with different NA inhibitors showed a synergistic effect (up to 4-fold) on cytopathic activity against influenza A-infected MDCK cells.
Resistance analysis of A/H1N1 and A/H3N2 strains showed that a single amino acid substitution of I38T in the PA coding region caused a 41-fold increase in the EC_{50} value of baloxavir. In addition, a substitution of E199G led to an increase in the EC_{50} value of baloxavir by 3-fold in A/H3N2 virus. The amino acid substitution in PA region in B virus strain was not detected *in vitro*.
Taken together, the results of the *in vitro* studies support the proposed mechanism of action of baloxavir and indicate that baloxavir has a potent antiviral activity against a broad panel of A and B influenza virus strains at concentrations below the clinical $C_{max,\ unbound}$ of 16 nM. The IC values of baloxavir for the inhibition of virus replication were lower than the values derived from biochemical data. This suggests that in addition to CEN inhibition another mechanism of action could also play a role. The reason for the higher efficacy in A strains could be the difference in five amino acid residues in CEN of influenza A and B viruses.
Higher efficacy of baloxavir on influenza A strains was also observed in *in vivo* studies. Nonlethal and lethal mice models were intranasally inoculated with various highly virulent influenza A (H1N1 and H3N2) and B strains. Immediate treatment of mice with baloxavir marboxil significantly reduced virus titres in the lungs of the infected mice and showed superiority to other antiviral agents. In mouse influenza models receiving lethal doses of virus strains, baloxavir significantly improved survival time, which correlated with the reduction of virus titres in the lung. Prolonged survival after delayed treatment was shown with baloxavir marboxil alone or in combination with oseltamivir (96 h). The results in immunocompromised mice showed superiority of baloxavir compared to oseltamivir. An immediate antiviral effect was also shown in ferrets.

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Taken together, the animal data support the antiviral activity of baloxavir marboxil at an exposure comparable to the clinical exposure. However, they are not predictive for the efficacy in human as the treatment schedule in humans is different (single dose).
Based on the results of the studies on secondary pharmacodynamics, the potential for off-target effects is considered to be low. Baloxavir has a high therapeutic index (≥ 500), resulting in maximum antiviral activity with minimal cell toxicity.
Baloxavir showed no specific toxicity on mitochondrial function.
Baloxavir marboxil had no adverse effects on the central nervous system or respiratory system in rats. In monkeys, no effects on the blood pressure, heart rate, or electrocardiogram (ECG) were observed.
Baloxavir marboxil had no effect on hERG current up to 10 µM, whereas the IC_{50} for baloxavir was estimated to be 7.31 µg/mL. There is no preclinical safety signal for cardiac toxicity in humans.

Pharmacokinetics
The pharmacokinetic (PK) profile of baloxavir marboxil was characterised in all nonclinical species (mice, rats, monkeys, and ferrets). After oral administration, baloxavir marboxil was rapidly hydrolysed to baloxavir and was therefore not detected in plasma or whole blood of any nonclinical species except ferrets. T_{max} was reached within 1 hour in rats and after 5.33 hours in monkeys, similar to the time in humans (4 h).
Plasma protein binding of baloxavir was similar in rats (92%), monkeys (85 to 89.5%), and humans (92.9 to 93.9%). The distribution ratios of baloxavir in blood cells were 57.1 to 59.6% in rats, 50.4 to 52.9% in monkeys, and 48.5 to 54.4% in humans.
A negative food effect on plasma exposure was observed in nonclinical species, as in humans. In cynomolgus monkeys, concomitant dosing with minerals and baloxavir marboxil resulted in a decrease in exposure of baloxavir. In rats and monkeys, bioavailability was approximately 10% under non-fasted conditions, and 10 and 50%, respectively, under fasted conditions.
After repeated dose administration of baloxavir marboxil once daily to rats, pregnant rabbits, and monkeys under non-fasted conditions, the C_{max} and $AUC_{0\text{-}24h}$ values of baloxavir in plasma increased less than dose proportionally.
Slower drug conversion of prodrug was observed in juvenile rats as baloxavir marboxil was detected in plasma. The exposure to baloxavir was also the highest in juvenile animals and increased dose-proportionally. The elimination rate increased with age.
Studies with oral administration of [^{14}C]-labelled baloxavir marboxil to pregnant albino and pigmented rats showed rapid and wide tissue distribution. The highest concentration was detected in the intestinal mucosa, followed by the liver and other organs of elimination. In most of the tissues the radioactivity was eliminated after 8 hours, although longer persistence of drug-related radioactivity was detected in the liver ($t_{1/2}$ 12.9 h), and bone ($t_{1/2}$ in bone 63.3 h). No radioactivity was detected in brain tissue. The radioactivity concentration in melanin-containing tissue was low and not detectable after 24 hours.
Radioactivity was observed in foetuses, suggesting that baloxavir crosses the placenta. Drug-related radioactivity in foetuses was eliminated within 48 hours, except for bones and skin; a prolonged retention in these tissues cannot be excluded.
Baloxavir marboxil was rapidly metabolised to baloxavir after incubation with S9 fraction from the liver or intestinal tract, and sera from rats, monkeys, and humans. Arylacetamide deacetylase (AADAC) was identified as the enzyme responsible for the hydrolysis. *In vivo* in rats and monkeys, baloxavir marboxil metabolites were primarily products of glucuronidation and oxidation of baloxavir; this is comparable with the metabolism in humans. The only metabolite detected at >10% in all species, including humans, was baloxavir glucuronide (16.4% in humans). As baloxavir glucuronide is an O-glucuronide, it is not considered to be of toxicological concern. Most drug-related radioactivity was excreted via bile/faeces, as in humans. Urinary excretion ratio was less than 1%. Baloxavir was detected in milk from lactating rats.

Toxicology
Studies to characterise the toxicological profile of baloxavir marboxil were conducted in rats, monkeys, and rabbits. The toxicology species selection is considered adequate since their PK is

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similar to that in humans. Animals were dosed orally with baloxavir marboxil once daily for up to 1 month under non-fasted conditions. The most common clinical observations in these studies were occasional gastrointestinal (GI) adverse findings (loose stools, diarrhoea and vomiting). GI findings in rats (80 mg/day dose) occurred at an exposure comparable to the clinical exposure and, in monkeys, approx. 8-fold above clinical exposure (AUC). The main target organ for toxicity in both species was the liver. In rats, hepatotoxicity was characterised by increases in liver weight with correlating gross pathology, histopathology, and increases in liver enzymes. In monkeys, no histopathological abnormalities were detected, although an increase in liver enzymes was observed. Although hepatotoxicity was observed at a clinically relevant exposure, the risk for humans is considered to be low, as single-dose administration of baloxavir marboxil is intended. A significant and dose-dependent, but reversible, decrease of colloid (minimal to mild) and hyperplasia of follicular epithelium in thyroid were observed in rats at clinically relevant exposures. A direct association with baloxavir marboxil cannot be excluded, as radioactively labelled baloxavir was also detected in the thyroid. However, the risk for humans is considered to be low due to the different treatment regimen.
Reversible testicular findings without clear dose dependency were observed in the 1-month study in monkeys (adhesion on the right testis/epididymis, marked fibrosis, and degeneration/necrosis in the seminiferous tubule).
The applicant provided historical control data to exclude a relationship with the treatment. The provided information is considered to be sufficiently satisfactory to conclude that no risk for humans is anticipated due to the single-dose treatment.
The significant prolongation of prothrombin time (PT) and increases in the activated partial thromboplastin time (APTT) in platelets and fibrinogen observed at ≥200 mg/kg in rats were not considered to be drug-related, as further investigational studies confirmed that this was a consequence of the fasting conditions and a reduction in vitamin K.
Baloxavir (marboxil) tested negative for genotoxicity *in vitro* and *in vivo*. Carcinogenicity studies were not conducted and are not necessary given the single-dose treatment.
Baloxavir marboxil did not have an effect on female or male fertility parameters in rats up to an exposure of 2.1-fold the clinical exposure. Embryo-foetal development studies were conducted in rats and rabbits. Decreases in maternal and foetal body weight were observed in both species at exposures 2-3 fold above the clinical exposure. In rabbits, the incidences of post-implantation losses and skeletal variations were also observed at 1000 mg/ml dose (exposure ratio 6.1). Skeletal variations (increased incidence of cervical ribs and a low incidence of full supernumerary ribs) were increased in high-dose rabbits. No malformations were observed.
In the pre- and post-natal development study in rats, enlargement of the eyeball with dark red discoloration was the only adverse finding. Since the finding was unilateral and occurred at a low frequency, this may not be drug-induced. Considering the single-treatment regime, the relevance for humans is considered to be negligible.
There were no adverse effects of baloxavir marboxil on the overall growth and development of juvenile rats at clinically relevant exposures. All adverse findings were also observed in adult rats. Overall, there are no safety margins, which is acceptable considering the single-dose treatment in humans. Baloxavir marboxil is not phototoxic. There are no concerns regarding impurities.
The submitted RMP includes an adequate description of the key safety findings from nonclinical studies and their relevance to humans. According to the environmental risk assessment, no significant risk for the environment is anticipated.

Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Xofluza with the new active substance baloxavir marboxil for the proposed indication. The pharmacological properties, as well as the PK and toxicity profiles for Xofluza, are considered to be adequately characterised. All nonclinical data relevant for human safety are included in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is adopting the results of the assessment of the foreign reference authority authority (see section 2.1. Applicant's request/Work-sharing procedure).

5.1 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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

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 1.13 mg sodium.
One 40 mg Xofluza film-coated tablet contains 155.8 mg lactose monohydrate and 2.26 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.

Indications/Uses

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours and who are:
• otherwise healthy, or
• at high risk of developing influenza-related complications.

Limitations of use

Baloxavir is not indicated for use as prophylaxis against influenza during a flu epidemic 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 sections *Properties/Effects, Clinical efficacy* and *Resistance monitoring during clinical development*).

Dosage/Administration

Usual dosage

A single dose of Xofluza should be taken within 48 hours of the onset of symptoms. Xofluza may be taken with or without food (see section *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.

Adults and adolescents (≥ 12 years of age)

Table 1 gives the recommended dose of Xofluza based on body weight.

Table 1 Xofluza dosing by patient weight

Patient body weight (kg)	Recommended single oral dose
40 kg to < 80 kg	40 mg
≥ 80 kg	80 mg

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 section *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 section *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 sections *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 of Xofluza has not been studied in patients aged < 12 years. Xofluza should not be used in these patients.

Mode of administration

Oral.

Contraindications

Xofluza is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or to any of its ingredients. Serious allergic reactions have been observed, including anaphylaxis, angio-oedema, urticarial, and erythema multiforme (see section *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 section *Undesirable effects*).
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”.

Interactions

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

Baloxavir marboxil did not cause malformations in rats or rabbits. High doses of baloxavir marboxil given to pregnant rabbits caused maternal toxicity, resulting in miscarriages and an increase in the incidence rates of minor skeletal abnormalities, but no malformations. No such effects were detected in rats (see section *Preclinical data, Reproductive toxicity*).

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

A decision should therefore be made on whether to discontinue nursing or 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 section *Preclinical data, Reproductive toxicity*).

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 2109 subjects in 17 clinical trials conducted with Xofluza. 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.

Undesirable effects after market launch

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 after market launch

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 stem 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 (EC_{90})) 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 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.

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

Clinical efficacy

Otherwise healthy 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 40kg) 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 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 2).

Table 2 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.

High risk patients

Capstone 2 (Study 1602T0832)

Study 1602T0832 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 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 2’182 patients were randomised to receive a single oral dose of 40 mg or 80 mg Xofluza depending on body weight (patients who weighed 40 to < 80 kg received 40 mg Xofluza and patients who weighed ≥ 80 kg received 80 mg), 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 2’182 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 3).

Table 3 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 statistically significantly shorter in the Xofluza group compared with the placebo group, but not compared with the oseltamivir group (see Table 4). In the patients infected with type B virus, the median time to improvement of the symptoms was statistically significantly shorter in the Xofluza group compared with both the placebo and oseltamivir group.

Table 4 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.

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.

Clinical studies: Influenza A virus isolates with treatment-emergent amino acid substitutions at position PA/I38T/F/M, associated with a > 10-fold reduction in susceptibility to baloxavir, were observed in clinical studies. The clinical relevance 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 or in the National Center for Biotechnology Information and the NCBI Influenza Virus Resource databases. Prescribers should consider available information from the 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 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 patients (5.2%) in the Xofluza treatment 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 5. 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 6.

Table 5 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 6 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.

Elimination

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 total radioactivity recovered in the faeces was 80.1% and 14.7% in urine. The amount of baloxavir excreted in the urine was 3.3% of the administered dose.
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 5 and 6.

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 identified as the significant covariate based on the population pharmacokinetic analysis. The recommended dose is 40 mg for adult patients with a body weight of 40 kg to < 80 kg, and 80 mg for adult patients with body weights ≥ 80 kg.

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 clinical studies conducted with baloxavir marboxil did not identify a clinically meaningful effect of age on the pharmacokinetics of baloxavir for subjects aged 12 to 64 years in relation to plasma baloxavir concentrations.

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

The pharmacokinetics of Xofluza have not been investigated in paediatric patients (aged < 12 years).

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 2 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 2 times the human exposure based on $AUC_{0\text{-}24h}$).
In rabbits, a dose of 1’000 mg/kg/day (equivalent to 6 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 3 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 2 times the human exposure based on $AUC_{0\text{-}24h}$).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

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 (Swissmedic)

Packs

Pack of 2 x 20 mg film-coated tablets (single use dose)
Pack of 4 x 20 mg film-coated tablets (single use dose)

Pack of 1 x 40 mg film-coated tablet (single use dose)
Pack of 2 x 40 mg film-coated tablets (single use dose)

Marketing authorisation holder

Roche Pharma (Schweiz) AG, Basel

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