Date: 18 February 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Xofluza

International non-proprietary name: baloxavirum marboxilum
Pharmaceutical form: film-coated tablet
Dosage strength: 40 mg and 20 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 67426
Decision and Decision date: approved on 19 November 2021

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 (Status as of 1 January 2020) 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
AE	Adverse event
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
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PEP	Post-exposure prophylaxis
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
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested to add to or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Prophylaxis of influenza

2.2.2 Approved Indication

Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 12 years and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as no relevant safety and efficacy studies have been conducted to date.
Prescribers should consider available information on influenza virus drug susceptibility patterns and relevant treatment effects (see "Properties/Effects, Clinical efficacy and Resistance monitoring during clinical development").

2.2.3 Requested Dosage

A single dose of Xofluza should be taken following close contact with a symptomatic person.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	1 July 2020
Formal control completed	22 July 2020
List of Questions (LoQ)	25 November 2020
Answers to LoQ	24 March 2021
Predecision	25 June 2021
Answers to Predecision	5 August 2021
Labelling corrections	16 November 2021
Answers to Labelling corrections:	17 November 2021
Final Decision	19 November 2021
Decision	approval

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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. Influenza virus is transmitted by direct or indirect contact with virus-containing respiratory fluids.

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

In Switzerland, influenza results in approximately 112,000 to 275,000 doctor's consultations, several thousand hospitalisations due to complications and several hundred deaths every year.

The risk of seasonal influenza infection can be reduced by the use of influenza vaccines.

(https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/grippe.html)

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4 Nonclinical Aspects

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

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information from these authorities were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology, see section 7.1 of this report.

5.2 Dose Finding and Dose Recommendation

No formal dose finding studies were performed. The approved dosing for treatment of influenza was used in the phase 3 study which evaluated the efficacy and safety of baloxavir in post-exposure prophylaxis.

5.3 Efficacy

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information from these authorities were used as a basis for the evaluation.

5.4 Safety

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information from these authorities were used as a basis for the evaluation.

5.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Influenza is caused by influenza A and influenza B viruses. Typical symptoms include fever, chills, coughing, sore throat or difficulty swallowing, headache, joint and muscle pain, runny nose, dizziness and a loss of appetite. Possible complications include upper respiratory tract infections, pneumonia and secondary bacterial infections. In Switzerland, influenza and its complications result in approximately 112,000 to 275,000 doctor’s consultations, several thousand hospitalisations and several hundred deaths every year.

BENEFICIAL EFFECTS
Baloxavir marboxil demonstrated efficacy in the prevention of influenza virus infection in study 1719T0834, a randomised, double-blind, placebo-controlled phase 3 study. The study included 749 subjects who were household members of influenza-infected patients who had been symptomatic for ≤ 48 hours. They received either baloxavir at the dose approved for treatment of influenza or placebo. Significantly fewer laboratory-confirmed influenza infections were observed in the group who received baloxavir marboxil (1.9%) as compared to the group who received placebo as post-exposure prophylaxis (13.6%).

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UNCERTAINTIES IN THE KNOWLEDGE ABOUT THE BENEFICIAL EFFECTS
Data on the efficacy and safety of baloxavir in post-exposure prophylaxis are only available from Japanese study participants. The efficacy results from study 1719T0834 were extrapolated to non-Asian subjects based on a PK bridging approach. Overall, baloxavir concentrations tend to be higher in Asian adults/adolescent patients compared to those in non-Asian adults/adolescent patients. However, this difference in exposure is not expected to impact efficacy and safety in prevention of infection.
The data from study 1719T0834 support efficacy in case of early initiation of prophylaxis (within 48 hours of symptom onset in the index case and even earlier, within 24 hours, for the majority of subjects). Efficacy in the case of >48 hours between symptom onset in the index case and Xofluza prophylaxis is unknown. This should be reflected adequately in the information for healthcare professionals.

UNFAVOURABLE EFFECTS
Baloxavir marboxil was generally well-tolerated and no unexpected safety findings were observed in the PEP study. The incidence of AEs was 22.2% (83/374 subjects, 102 events) in the baloxavir marboxil group and 20.5% (77/375 subjects, 99 events) in the placebo group. The incidence of treatment-related AEs was 1.9% (7/374 subjects, 7 events) in the baloxavir marboxil group and 1.6% (6/375 subjects, 7 events) in the placebo group. The incidence of AEs and treatment-related AEs was similar between the treatment groups. No deaths were reported.
The most frequently reported AEs were nasopharyngitis, headache, presence of blood in urine, pharyngitis and increased ALT. Presence of blood in urine, pharyngitis and increased ALT were reported more frequently in the baloxavir marboxil group than in the placebo group.

BENEFIT-RISK ASSESSMENT
Based on the demonstrated efficacy in the prevention of influenza infection and the relatively good safety profile, the benefit/risk assessment for post-exposure prophylaxis of influenza in persons aged 12 years and older is positive.

5.6 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 Xofluva 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

Treatment of Influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and above who have been symptomatic for no more than 48 hours and who are:

- otherwise healthy, or
- 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 12 years and above. Xofluza is not indicated for use as pre-exposure prophylaxis against influenza as no relevant safety and efficacy studies have been conducted to date.

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

Dosage/Administration

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 baloxavir marboxil should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza.

General Information

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.

Usual dosage

Treatment or Post-Exposure Prophylaxis of adults and adolescents (≥ 12 years of age)

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

Table 1: Xofluza dosing by weight for adults and adolescents (≥ 12 years of age)

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 «*Pharmacokinetics, Kinetics in specific patient groups, Hepatic impairment*»). Xofluza has not been studied in patients with severe hepatic impairment.

Patients with impaired renal function

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

Elderly patients

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

Children (<12 years of age)

The safety and efficacy of Xofluza has not been established 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 «*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*»).
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, inhibitors or inducers of cytochrome P450 (CYP enzymes), substrates or inhibitors of UDP-glucuronosyltransferase (UGT) enzyme, or gut, renal, or hepatic transporters.

Pharmacokinetic interactions

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

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

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

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

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

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

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

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

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

Immune response

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

Pregnancy, lactation

Pregnancy

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

Labour and delivery

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

Lactation

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

Fertility

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

Effects on ability to drive and use machines

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

Undesirable effects

The overall safety profile of Xofluza is based on data from 19 clinical studies.

Treatment of Influenza

No adverse drug reactions were identified based on pooled data from 3 placebo-controlled clinical studies (studies 1518T0821, 1601T0831 and 1602T0832) carried out in adult and adolescent patients, in which a total of 1640 patients were given Xofluza.

This includes otherwise healthy adults and adolescents, as well as patients at high risk of developing complications associated with influenza, e.g. elderly patients and patients with chronic cardiac or respiratory disease. 1’334 patients (81.3%) were adults aged ≥ 18 to ≤ 64 years, 209 patients (12.7%) were adults aged ≥ 65 years, and 97 patients (5.9%) were adolescents (aged ≥ 12 to < 18 years). Of these 1’640 patients, 1’440 patients received Xofluza at a dose of 40 mg or 80 mg and 100 patients each received a dose of 10 mg or 20 mg. The safety profile in patients at high risk was similar to that in otherwise healthy adults and adolescents.

No adverse drug reactions have been identified in children 1 to < 12 years of age based on one active controlled, double-blind study (CP40563), in which a total of 115 patients received the recommended dosage of Xofluza.

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, Prophylaxis of Infuenza, BLOCKSTONE (Study 1719T0834)*»).

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

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

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

Clinical efficacy

Treatment of Influenza

Otherwise Healthy Adult and Adolescent Patients

CAPSTONE-1 (Study 1601T0831)

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

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

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 3: 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)

High Risk Patients

CAPSTONE-2 (Study 1602T0832)

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

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

A total of 2’184 patients were randomised to receive a single oral dose of 40 mg or 80 mg Xofluza depending on body weight (40 to < 80 kg or ≥ 80 kg respectively), oseltamivir 75 mg twice daily for 5 days, or placebo. The predominant influenza viruses in this study were the A/H3 subtype (46.9% to 48.8%) and influenza type B (38.3% to 43.5%). Of these patients, 43% were Asian, 46% White and 10% Black or African American (1% other). The majority of patients had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity or were aged 65 or older. In this study, 1’158 of the 2’184 patients who were enrolled had influenza confirmed by RT-PCR and were included in the

efficacy analysis (Xofluza n=385, placebo n=385 or oseltamivir n=388). The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue). This endpoint included the alleviation of new symptoms and improvement of any pre-existing symptoms that had deteriorated due to influenza. A statistically significant improvement in the primary endpoint was observed for Xofluza when compared with placebo (see Table 4).

Table 4: Time to Improvement of Influenza Symptoms (Xofluza vs Placebo)

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

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

Virus subtype

For patients infected with the subtype A/H3 virus (predominant strain), the median time to improvement of the symptoms was shorter in the Xofluza group compared with the placebo group, but not compared with the oseltamivir group (see Table 5). 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 5: 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]	100.6 [82.8, 115.8]	101.6 [90.5, 114.9]

	N=166	N=167	N=148

Incidence of influenza-related complications

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

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 received either baloxavir marboxil dosed according to weight, as in the treatment studies, or placebo. The majority (74%) was 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 (46.2%) followed by influenza B (0.9%). There were 142 subjects under 12 years of age, who were dosed according to body weight. 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 6).

Table 6: 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	N=304 13.2		

(0.4, 3.3)	(9.6, 17.5)		
Proportion of Subjects <12 years with Influenza Virus, Fever, and at least one Respiratory Symptom (%)*			
N=71 4.2 (0.9, 11.9)	N=71 15.5 (8.0, 26.0)		

* Based on subgroup analysis

Resistance monitoring during clinical development

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

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

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

In the phase 3 study conducted in otherwise healthy patients (1601T0831), the amino acid substitution PA/I38T/M was detected in 36 of 370 influenza-infected patients (9.7%) in the Xofluza treatment group. In the phase 3 study conducted in high risk patients (1602T0832), the amino acid substitution PA/I38T/M/N was detected in 15 of 290 influenza-infected patients (5.2%) in the Xofluza treatment group. In the phase 3 study conducted in paediatric patients (CP40563), the amino acid substitution PA/I38T/M/S was detected in 11 of 57 influenza-infected patients (19.3%) in the Xofluza treatment group. In the prophylactic study (1719T0834), the amino acid substitution PA/I38T/M was detected in 10 of 374 subjects (2.7%) in the Xofluza group.

Cross-resistance

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

Pharmacokinetics

Absorption

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

The pharmacokinetic parameters for baloxavir in healthy Japanese adults after a single oral administration of 40 mg baloxavir marboxil in the fasting and postprandial states are summarised in Table 7. 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 8.

Table 7: 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 8: Pharmacokinetic Parameters for Baloxavir in the Plasma in Healthy Caucasian Adults after Administration of a Single Oral Dose of 80 mg of Baloxavir Marboxil in the Fasting State (Study 1612T081C)

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

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

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

Distribution

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

Metabolism

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

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

Excretion

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

Elimination

The apparent terminal elimination half-life ($t_{1/2,z}$) for baloxavir after a single oral administration of baloxavir marboxil is 79.1 hours in Caucasian patients, and 93.9 hours in Japanese subjects, see Tables 7 and 8.

Linearity/non-linearity

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

Kinetics in specific patient groups

Body weight

Body weight was a significant covariate based on the population-related pharmacokinetic analysis. The dosage was therefore adjusted to body weight in both adult and adolescent subjects. In adults and in adolescents, the dose is 40 mg for a body weight of 40 kg to < 80 kg and 80 mg for a body weight of ≥ 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 baloxavir plasma concentrations in patients aged 12 to 64 years who received baloxavir marboxil in clinical studies did not identify age as a clinically relevant covariate for the pharmacokinetics of baloxavir.

Hepatic impairment

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

Renal impairment

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

Elderly patients

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

Children and adolescents

The pharmacokinetics of Xofluza have not been investigated in paediatric patients below 12 years of age.

Preclinical data

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

Mutagenicity

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

Carcinogenicity

No carcinogenicity studies have been conducted with baloxavir marboxil.

Reproductive toxicity

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

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

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

Other information

Shelf life

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

Special precautions for storage

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

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 (Swissmedic).

Packs

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

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

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