SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Xofluza 2 mg/mL granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 2 mg of baloxavir marboxil.

One bottle contains 40 mg of baloxavir marboxil.

Excipients with known effect

Each 20 mL of oral suspension contains 1.03 mmol (or 23.6 mg) sodium and 700 mg of maltitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension.

White to light yellow granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 3 weeks and above.

Post-exposure prophylaxis of influenza

Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 3 weeks and above.

Xofluza should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Treatment of influenza
A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours of symptom(s) onset.

Post-exposure prophylaxis of influenza
A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza (see section 5.1).

Adults, adolescents, children and infants (≥ 3 weeks of age)
The recommended single oral dose of baloxavir marboxil is determined by body weight (see Table 1).

Adults, adolescents and children weighing ≥ 20 kg who are able to swallow tablets may instead receive treatment with Xofluza tablets at a dose of 40 mg or 80 mg depending on the patient's body weight. Refer to the Xofluza tablet SmPC for dose information.

Table 1. Baloxavir marboxil dosing by patient body weight (≥ 3 weeks of age)

Patient body weight (kg)	**Recommended single dose of oral suspension**	**Volume of oral suspension***
< 20 kg	2 mg per kg of body weight	1 mL per kg of body weight
≥ 20 kg to < 80 kg	40 mg	20 mL
≥ 80 kg	80 mg	40 mL**

* The volume of the suspension in the bottle after reconstitution is 22 mL. The exact volume to be administered should be measured using the oral dispenser(s) included in the carton. e.g., 20 mL of suspension provides the recommended single dose of 40 mg.
**Dose requires 2 bottles of Xofluza granules for oral suspension.

There are no clinical data on the use of a repeat dose of baloxavir marboxil for the treatment of uncomplicated influenza or for post-exposure prophylaxis in any one influenza season.

Special populations

Elderly
No dose adjustment is required (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh class A or B). The safety and efficacy of baloxavir marboxil have not been established in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of baloxavir marboxil in preterm neonates and children aged < 3 weeks have not been established. No data are available.

Method of administration

Oral or enteral use.
Xofluza may be taken with or without food (see section 5.2). Granules for oral suspension and final oral suspension should not be mixed with food. Any mixing outside the recommendations is the responsibility of the healthcare professional or the user.

Xofluza should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium (see section 4.5).It is recommended that Xofluza granules for oral suspension be reconstituted by a healthcare professional prior to dispensing. If the patient or caregiver is reconstituting the oral suspension, they must be advised to read the instructions for use before preparing and administering.

For instructions on re constitution of Xofluza granules before administration, see section 6.6.

The appearance after reconstitution is a greyish white, white to light yellow opaque suspension.

The recommended dose can be administered via an enteral feeding tube. The tube should be flushed with water before and after delivering Xofluza. Follow the manufacturer's instructions for the feeding tube to administer the medicine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Sodium

This medicinal product contains 23.6 mg of sodium per 20 mL of oral suspension, equivalent to 1.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Maltitol

This medicinal product contains 700 mg of maltitol per 20 mL of oral suspension. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on baloxavir marboxil or its active metabolite baloxavir

Products that contain polyvalent cations may decrease plasma concentrations of baloxavir. Xofluza should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium.

Immune response to influenza virus

Interaction studies with influenza vaccines and baloxavir marboxil have not been conducted. In studies of naturally acquired influenza, treatment with Xofluza did not impair the humoral antibody response to influenza infection.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of baloxavir marboxil in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Xofluza during pregnancy.

Breast-feeding

It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk. Baloxavir marboxil and its metabolites are secreted in the milk of lactating rats.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to abstain from Xofluza therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No effects on male or female fertility were observed in animal studies performed with baloxavir marboxil (see section 5.3).

4.7 Effects on ability to drive and use machines

Xofluza has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity reactions have been observed in the post-marketing setting, which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions, including urticaria and angioedema. Of these adverse reactions only urticaria has been observed in clinical studies with an estimated frequency category of “uncommon”.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified from post-marketing experience with baloxavir marboxil (Table 2) based on spontaneous case reports and cases from non-interventional study programmes. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2. Adverse drug reactions from post-marketing experience in adults, adolescents and paediatric patients

System organ class (SOC)	Adverse reaction (preferred term (PT), MedDRA)	Frequency
Immune system disorders	Anaphylaxis[a]	Not known
	Anaphylactic reactions[a]	Not known
	Hypersensitivity[a]	Not known
Gastrointestinal disorders	Diarrhoea[b]	Common
	Vomiting[b]	Common
Skin and subcutaneous disorders	Urticaria[b]	Uncommon
	Angioedema[a]	Not known

[a]Not reported in clinical studies.
[b]The frequency calculation is based on completed clinicalstudies.

Paediatric population

The safety profile of baloxavir marboxil in paediatric patients (3 weeks to < 12 years) was determined from data collected from treatment and post-exposure prophylaxis studies. Table 3 presents adverse drug reactions identified from clinical trial experience.

Anaphylactic reaction, anaphylaxis, urticaria and angioedema (face, eyelid and lip swelling) have been reported post-marketing in the paediatric population (see Table 2).

Table 3. Adverse drug reactions in children from clinical trial experience

System organ class (SOC)	Adverse reaction (preferred term (PT), MedDRA)	Frequency
Gastrointestinal disorders	Diarrhoea	Common
	Vomiting	Common
Skin and subcutaneous disorders	Rash	Common

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of overdoses with baloxavir marboxil have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse reactions were reported. Data are insufficient to determine what symptoms may be anticipated as a result of an overdose.

Management

No known specific antidote exists for Xofluza. In the event of 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other anti-virals. ATC code: J05AX25.

Mechanism of action

Baloxavir marboxil is a prodrug that is converted by hydrolysis to 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 inhibition of influenza virus replication.

In vitro activity

The 50 % inhibition 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.

In a MDCK cell culture assay, the median 50 % effective concentration (EC_{50}) values of baloxavir were 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 titre reduction assay, the 90 % effective concentration (EC_{90}) values of 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.

Resistance

Viruses bearing PA/I38T/F/M/N/S mutations or the PA/T20K mutation selected *in vitro* or in clinical studies show reduced susceptibility to baloxavir. PA/I38T/F/M/N/S mutations led to an increase in EC_{50} values ranging from 11 to 57-fold for influenza A viruses and 2 to 8-fold for influenza B viruses. The PA/T20K mutation led to a 7-fold increase in the EC_{50} value for influenza B virus.

In the four phase 3 studies of treatment of uncomplicated influenza (see below) no resistance to baloxavir was detected in baseline isolates. In the two adult and adolescent studies, treatment -emergent mutations PA/I38T/M/N were detected in 36/370 (9.7 %) and in 15/290 (5.2 %) patients treated with baloxavir marboxil but were not detected in any patients treated with placebo.

In the phase 3 study in paediatric patients aged 1 to < 12 years (Ministone-2 (CP40563)), treatment-emergent mutations, PA/I38T/M/S were found in 11 of 57 (19.3 %) influenza-infected subjects in the baloxavir marboxil treatment group.

In the phase 3 study in paediatric patients aged < 1 year (Ministone-1 (CP40559)), PA/I38T and PA/T20K were detected in 2 of 13 (15.4 %) influenza-infected subjects treated with baloxavir marboxil.

In the phase 3 study of post-exposure prophylaxis (see below), PA/I38T/M were found in 10 of 374 (2.7 %) baloxavir marboxil-treated subjects. PA/I38 substitutions were not detected in placebo-treated subjects, with the exception of 2 subjects who received baloxavir marboxil as rescue medication.

Baloxavir is active *in vitro* against influenza viruses that are considered resistant to neuraminidase inhibitors, including strains with the following mutations: H274Y in A/H1N1, E119V and R292K in A/H3N2, R152K and D198E in type B virus, H274Y in A/H5N1, R292K in A/H7N9.

Clinical trials

Treatment of uncomplicated influenza

Adult and adolescent patients

Capstone 1 (1601T0831) was a phase 3 randomised, double-blind, multicentre study conducted in Japan and the US to evaluate the efficacy and safety of a single oral tablet dose of baloxavir marboxil compared with placebo and with oseltamivir in healthy adult and adolescent patients (aged ≥ 12 years to ≤ 64 years) with uncomplicated influenza. Patients were randomised to receive baloxavir marboxil (patients who weighed 40 to < 80 kg received 40 mg and patients who weighed ≥ 80 kg received 80 mg), oseltamivir 75 mg twice daily for 5 days (only if aged ≥ 20 years) or placebo. Dosing occurred within 48 hours of first onset of symptoms.

A total of 1436 patients (of which 118 were aged ≥ 12 years to ≤ 17 years) were enrolled in the 2016-2017 Northern Hemisphere influenza season. 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 %). The

primary efficacy endpoint was time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) (TTAS).

Baloxavir marboxil elicited a statistically significant reduction in TTAS when compared with placebo (Table 4).

Table 4. Capstone 1: Time to alleviation of symptoms (baloxavir marboxil vs placebo), ITTI population*

Time to alleviation of symptoms (Median [hours])			
Baloxavir marboxil 40/80 mg (95 % CI) N=455	**Placebo (95 % CI) N=230**	**Difference between Baloxavir marboxil 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

*ITTI: The Intention-to-treat Infected population consisted of patients who received the study medicine with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of RT-PCR on Day 1.

When the baloxavir marboxil group was compared to the oseltamivir group, there was no statistically significant difference in TTAS (53.5 h vs 53.8 h, respectively).

The median (95 % CI) TTAS was 49.3 (44.0, 53.1) and 82.1 (69.5, 92.9) hours for patients who were symptomatic for > 0 to ≤ 24 hours, and 66.2 (54.4, 74.7) and 79.4 (69.0, 91.1) hours for patients who were symptomatic for > 24 to ≤ 48 hours for baloxavir marboxil and placebo, respectively.

The median time to resolution of fever in patients treated with baloxavir marboxil was 24.5 hours (95 % CI: 22.6, 26.6) compared with 42.0 hours (95 % CI: 37.4, 44.6) in those receiving placebo. No difference was noted in duration of fever in the baloxavir marboxil group compared with the oseltamivir group.

Capstone 2 (1602T0832) was a phase 3 randomised, double-blind, multicentre study to evaluate the efficacy and safety of a single oral tablet dose of baloxavir marboxil compared with placebo and with oseltamivir in adult and adolescent patients (aged ≥ 12 years) with uncomplicated influenza who had at least one host factor predisposing to the development of complications. Patients were randomised to receive a single oral dose of baloxavir marboxil (according to weight as in Capstone 1), oseltamivir 75 mg twice daily for 5 days, or placebo. Dosing occurred within 48 hours of first onset of symptoms.

Of the total 2184 patients 59 were aged ≥ 12 to ≤ 17 years, 446 were aged ≥ 65 to ≤ 74 years, 142 were aged ≥ 75 to ≤ 84 years and 14 were aged ≥ 85 years. The predominant influenza viruses in this study were the A/H3 subtype (46.9 % to 48.8 %) and influenza B (38.3 % to 43.5 %). The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) (TTIS). Baloxavir marboxil elicited a statistically significant reduction in TTIS when compared with placebo (Table 5).

Table 5. Capstone 2: Time to improvement of influenza symptoms (baloxavir marboxil vs placebo), ITTI population

Time to improvement of influenza symptoms (Median [hours])			
Baloxavir marboxil 40/80 mg (95 % CI) N=385	Placebo (95 % CI) N=385	Difference between Baloxavir marboxil and placebo (95 % CI for difference)	P-value
73.2 (67.2, 85.1)	102.3 (92.7, 113.1)	-29.1 (−42.8, −14.6)	< 0.0001

When the baloxavir marboxil group was compared to the oseltamivir group, there was no statistically significant difference in TTIS (73.2 h vs 81.0 h respectively).

The median (95 % CI) TTIS was 68.6 (62.4, 78.8) and 99.1 (79.1, 112.6) hours for patients who were symptomatic for > 0 to ≤ 24 hours and 79.4 (67.9, 96.3) and 106.7 (92.7, 125.4) hours for patients who were symptomatic for > 24 to ≤ 48 hours for baloxavir marboxil and placebo, respectively.

For patients infected with type A/H3 virus, the median TTIS was shorter in the baloxavir marboxil group compared with the placebo group but not compared with the oseltamivir group (see Table 6). In the subgroup of patients infected with type B virus, the median TTIS was shorter in the baloxavir marboxil group compared with both the placebo and oseltamivir group (see Table 6).

Table 6. Time to improvement of symptoms by influenza virus subtype, ITTI population

Time to improvement of symptoms (Hours) **Median [95 % CI]**			
Virus	**Baloxavir marboxil**	**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

The median time to resolution of fever was 30.8 hours (95 % CI: 28.2, 35.4) in the baloxavir marboxil group compared with 50.7 hours (95 % CI: 44.6, 58.8) in the placebo group. No clear differences between the baloxavir marboxil group and the oseltamivir group were observed.

The overall incidence of influenza-related complications (death, hospitalisation, sinusitis, otitis media, bronchitis, and/or pneumonia) was 2.8 % (11/388 patients) in the baloxavir marboxil group compared with 10.4 % (40/386 patients) in the placebo group. The lower overall incidence of influenza-related complications in the baloxavir marboxil group compared with the placebo group was mainly driven by lower incidences of bronchitis (1.8 % vs. 6.0 %, respectively) and sinusitis (0.3 % vs. 2.1 %, respectively).

Paediatric patients (aged 1 - < 12 years)

Ministone-2 (CP40563) was a randomised, double-blind, multicentre, active-controlled study, designed to evaluate the safety, efficacy, and pharmacokinetics of a single oral dose of granules for oral suspension of baloxavir marboxil compared with oseltamivir in otherwise healthy paediatric patients (aged 1 to < 12 years) with influenza-like symptoms.

A total of 173 patients were randomised 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. Patients could receive paracetamol as required. Patients with host factors predisposing to the development of complications (14 % (25/173)) were included in the study. 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 5 days of oseltamivir administered twice daily. 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 return to normal health and activity and duration of fever).

Time to alleviation of influenza signs and symptoms were comparable between the baloxavir marboxil group (median 138.1 hours [95 % CI: 116.6, 163.2]) and the oseltamivir group (median 150 hours [95 % CI: 115.0, 165.7]) see Table 7.

Table 7. Time to alleviation of influenza signs and symptoms, ITTI population

Time to alleviation of symptoms (Median [hours])	
Baloxavir marboxil **(95 % CI)** **N=80**	**Oseltamivir** **(95 % CI)** **N=43**
138.1 (116.6, 163.2)	150.0 (115.0, 165.7)

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

The overall incidence of influenza-related complications (death, hospitalisation, pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) was 7.4 % (6/81 patients) in the baloxavir marboxil group and 7 % (3/43 patients) in the oseltamivir group. The incidence of otitis media was 3.7 % (3/81 patients) in the baloxavir marboxil group and 4.7 % (2/43 patients) in the oseltamivir group. Sinusitis, pneumonia and bronchitis occurred in one patient each in the baloxavir marboxil group and febrile seizures occurred in one patient in the oseltamivir group.

Paediatric patients (aged < 1 year)

Ministone-1 (CP40559) was a multicenter, single-arm, open label study to evaluate the safety, pharmacokinetics and efficacy of a single oral dose of baloxavir marboxil in paediatric patients (aged < 1 year) with influenza-like symptoms. The youngest patient recruited was 3 weeks of age. Extrapolation of efficacy to < 1 year was based on exposure matching from adults and older children.

A total of 48 patients received a single oral dose of baloxavir marboxil based on body weight and age (2 mg/kg for patients ≥ 3 months (N=39), 1 mg/kg for patients ≥ 4 weeks to < 3 months (N=8) and 1 mg/kg for patients <4 weeks (N=1)). The predominant influenza virus strain in this study was the A/H3 subtype. The primary objective was to evaluate the safety and PK of a single oral dose of baloxavir marboxil. A secondary objective was to evaluate the efficacy of baloxavir marboxil based on the efficacy endpoints including time to alleviation of influenza signs and symptoms (cough and nasal symptoms, time to return to normal health and activity and duration of fever). No new safety concerns were identified.

Post-exposure prophylaxis of influenza

Blackstone (1719T0834) was a phase 3, randomised, double-blind, multicentre study conducted in 749 subjects in Japan to evaluate the efficacy and safety of a single oral tablet dose or a single dose of granules of baloxavir marboxil compared with placebo for post-exposure prophylaxis of influenza. Subjects were household contacts of influenza-infected index patients.

There were 607 subjects ≥12 years and 142 subjects 1 to < 12 years who received either baloxavir marboxil dosed according to weight, as in the treatment studies, or placebo. The majority of subjects (73.0 %) were enrolled within 24 hours of symptom onset in the index patient group. The predominant influenza virus strains in the index patients were the A/H3 subtype (48.6 %) and the A/H1N1pdm subtype (47.5 %) followed by influenza B (0.7 %).

The primary efficacy endpoint was the proportion of household subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

There was a statistically significant reduction in the proportion of subjects with laboratory-confirmed clinical influenza from 13.6 % in the placebo group to 1.9 % in the baloxavir marboxil group (see Table 8).

Table 8. Proportion of subjects with influenza virus, fever, and at least one respiratory symptom (baloxavir vs placebo)

Proportion of subjects with influenza virus, fever, and at least one respiratory symptom (%) mITT[*] population			
Baloxavir marboxil (95 % CI)	**Placebo (95 % CI)**	**Adjusted risk ratio (95 % CI)**	**P-value**
N=374 1.9 (0.8, 3.8)	N=375 13.6 (10.3, 17.5)	 0.14 (0.06, 0.30)	< 0.0001
Proportion of subjects ≥ 12 years with influenza virus, fever, and at least one respiratory symptom (%)			
N=303 1.3 (0.4, 3.3)	N=304 13.2 (9.6, 17.5)	 0.10 (0.04, 0.28)	< 0.0001
Proportion of subjects 1 to < 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, 26)	 0.27 (0.08, 0.90)	0.0339

* mITT: modified intention-to-treat. The mITT population included all randomised subjects who received the study medicine and had post-baseline efficacy data available among household members of influenza-infected index patients. The mITT population was analysed as randomised.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xofluza

in one or more subsets of the paediatric population for the treatment of influenza and prevention of influenza (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration, baloxavir marboxil is extensively converted to its active metabolite, baloxavir. The plasma concentration of baloxavir marboxil is very low or below the limit of quantitation (< 0.100 ng/mL).

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

In adults after single administration of baloxavir marboxil at the therapeutic doses, the estimated mean baloxavir $AUC_{0\text{-}inf}$ were 9580 and 4750 ng.hr/mL, and the estimated mean C_{max} were 95.2 and 62.4 ng/mL in the Asian and non-Asian populations, respectively.

Following a single oral administration of 80 mg of baloxavir marboxil, the time to achieve peak plasma concentration (T_{max}) is approximately 4 hours in the fasted state. The absolute bioavailability of baloxavir after oral dosing with baloxavir marboxil has not been established.

Food effect

In a food-effect study after administration of baloxavir marboxil at a 40 mg dose to healthy volunteers, C_{max} and $AUC_{0\text{-}inf}$ of baloxavir were decreased by 48 % (geometric mean (CV %) of 67.6 (40.0) vs 130 (24.1) ng/mL) and 36 % (geometric mean (SD) of 4540 (38.8) vs 7090 (19. 6) ng.hr/mL), in fed (with a meal of approximately 400 to 500 kcal including 150 kcal from fat) relative to fasting conditions, respectively. T_{max} was unchanged in the presence of food. In clinical studies there were no clinically relevant differences in efficacy when baloxavir was taken with versus without food.

Distribution

In an *in-vitro* study, the binding of baloxavir to human serum proteins, primarily albumin, is 92.9 % to 93.9 %. The apparent volume of distribution of baloxavir during the terminal elimination phase (Vz/F) following a single oral administration of baloxavir marboxil is approximately 1180 L in Caucasian subjects and 647 L in Japanese subjects. The population PK parameter estimates were 260 L for the apparent peripheral volume of distribution, and 489 L and 735 L for the apparent central volume of distribution in the Asian and non-Asian populations, respectively.

Biotransformation

Baloxavir is primarily metabolised by UGT1A3 to form a glucuronide with a minor contribution from CYP3A4 to form a sulfoxide.

Drug-drug interaction studies

Based on *in vitro* and *in vivo* drug-drug interaction (DDI) studies, baloxavir marboxil and baloxavir are not expected to inhibit isozymes of the CYP or UGT families or cause relevant induction of CYP enzymes.

Based on *in vitro* transporter studies and *in vivo* DDI studies, no relevant pharmacokinetic interaction is anticipated between baloxavir marboxil or baloxavir and medicines which are substrates of the following transporters: OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

Excretion

Following a single oral administration of 40 mg of [^{14}C]-labeled baloxavir marboxil, the proportion of total radioactivity excreted in faeces was 80.1 % of the administered dose, with the urine accounting for 14.7 % (3.3 % and 48.7 % of the administered dose was excreted as baloxavir in urine and faeces respectively).

Elimination

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

The apparent terminal elimination half-life ($t_{1/2,z}$) of baloxavir after a single oral administration of baloxavir marboxil is 79.1, 50.3 and 29.4 hours in Caucasian adults, adolescent and paediatric subjects, respectively.

Linearity/non-linearity

Following single oral administration of baloxavir marboxil, baloxavir exhibits linear pharmacokinetics within the dose range of 6 mg to 80 mg.

Special populations

Body weight

Body weight is a significant covariate for baloxavir pharmacokinetics based on the population pharmacokinetic analysis, independently of age. Dosing recommendations for baloxavir marboxil are based on body weight in both adult and paediatric patients (see section 4.2).

Gender

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

Race

Based on a population pharmacokinetic analysis, race is an age-independent covariate on oral clearance (CL/F) of baloxavir in addition to body weight; however, no dose adjustment of baloxavir marboxil based on race is required.

Age

A population pharmacokinetic analysis using plasma baloxavir concentrations from clinical studies in subjects aged 1 to 64 years did not identify age as a relevant covariate on the pharmacokinetics of baloxavir. In a population PK analysis including 57 paediatric patients under 1 year of age, age significantly influenced baloxavir CL/F; a maturation half-life of 38.3 weeks was estimated. However, no dose adjustment of baloxavir marboxil based on age is required.

Paediatric population

Pharmacokinetic data of baloxavir were collected in patients aged 3 weeks to < 12 years. The body weight-adjusted dosing regimen (2 mg/kg up to 20 kg and 40 mg for ≥ 20 kg) provides similar baloxavir exposures to the therapeutic doses of baloxavir marboxil in adults (40 mg for adult patients < 80 kg and 80 mg for adult patients ≥ 80 kg) in both Asian and non-Asian populations (see Table 9).

The pharmacokinetics of baloxavir in paediatric patients below 3 weeks of age have not been established.

Table 9. Mean (5^{th} – 95^{th} percentile) pharmacokinetic parameters of baloxavir in non-Asian patients aged 3 weeks and above receiving a single oral baloxavir marboxil administration

Age group	Dose group*	N	$AUC_{0\text{-}inf}$ (ng.hr/mL)	C_{max} (ng/mL)	C_{72} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
22 - < 28 days	1 mg/kg**	1	2640 [NA,NA]	66.9 [NA,NA]	8.71 [NA,NA]	5 [NA,NA]	23.4 [NA,NA]
28 days - <3 months	1 mg/kg**	8	2580 [864,4880]	57.1 [37.1,80.4]	9.53 [1.3,20.3]	6.5 [2,13]	25.2 [13,32.8]
3 months - < 1 year	2 mg/kg	37	5670 [1800,11900]	144 [48.8,294]	18.4 [4.43,41.5]	5.09 [2,13]	22.9 [15.5,30.3]
1 - < 2 years	2 mg/kg	8	3260 [1670,5970]	95.5 [33.1,215]	10.0 [2.02,14.2]	3.56 [1.5,7]	23 [11.6,38.8]
2 - < 12 years	2 mg/kg	32	4490 [765,9070]	116 [21.4,272]	15.0 [3.06,32.2]	3.94 [1.5,7.5]	24.2 [17.4,35.3]
	40 mg	64	4650 [1770,9130]	87.1 [31.1,147]	19.1 [7.36,39.2]	5.51 [2.5,10.5]	33.8 [21.7,52.4]
12 - < 18 years	40 mg	44	3520 [1230,7470]	52.7 [17.5,94.3]	15.5 [5.76,31.2]	4.32 [1.5,7.5]	42.9 [32,69]
	80 mg	13	6600 [2730,11600]	83.7 [43.9,147]	29.6 [12.1,51.7]	5.19 [1,13]	50.7 [34.2,64.5]
18 years and above	40 mg	310	3470 [1440,6350]	47.4 [20.6,86.2]	15.4 [6.36,27.8]	4.67 [1.5,10]	47.7 [31.2,67.5]
	80 mg	338	5880 [2270,11200]	73.4 [27.5,141]	26.2 [10.7,49.4]	5.19 [2,11]	52.8 [33.6,76.2]

* Dose groups are based on bodyweight: < 20 kg: 2 mg/kg; ≥ 20 kg - < 80 kg: 40 mg; ≥ 80 kg: 80 mg; ** For age categories with no PK observations at the recommended dose of baloxavir marboxil, population-PK modeling predicts that a dose of 2 mg/kg in children 22 days to 3 months of age produces a similar exposure as adults and older children.

Elderly

Pharmacokinetic data collected in 181 patients aged ≥ 65 years show that exposure to baloxavir in the plasma was similar to that in patients aged ≥ 12 to 64 years.

Hepatic impairment

No clinically meaningful differences in the pharmacokinetics of baloxavir were observed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B) compared with healthy controls with normal hepatic function.

The pharmacokinetics in patients with severe hepatic impairment have not been evaluated (see section 4.2).

Renal impairment

The effects of renal impairment on the pharmacokinetics of baloxavir marboxil or baloxavir have not been evaluated. Renal impairment is not expected to alter the elimination of baloxavir marboxil or baloxavir.

5.3 Preclinical safety data

Nonclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity.

Prolongation of PT and APTT were observed in rats at exposures at least equal to the human exposure based on $AUC_{0\text{-}24hr}$ under specific experimental conditions, i.e. when fasted and when the food was either autoclaved or radiation-treated, resulting in vitamin K limiting/deficient conditions. These effects were not observed in monkey studies up to 4 weeks duration at the highest tested dose equivalent to 8-times the human exposure based on $AUC_{0\text{-}24hr}$. They are considered to be of limited clinical relevance.

Carcinogenicity studies have not been performed with baloxavir marboxil.

The pro-drug baloxavir marboxil, and its active form, baloxavir, were not considered genotoxic as they tested negative in bacterial reverse mutation tests, micronucleus tests with cultured mammalian cells, and as baloxavir marboxil was negative in an *in vivo* rodent micronucleus test.

Baloxavir marboxil had no effects on fertility when given orally to male and female rats at doses providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr.}$

Baloxavir marboxil did not cause malformations in rats or rabbits.

The oral embryo-foetal development study of baloxavir marboxil in rats with daily doses from gestation Day 6 to 17 revealed no signs of maternal or foetal toxicity up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr.}$

In rabbits, a dose providing exposure equivalent to 14-times the human exposure based on $AUC_{0\text{-}24hr}$ following the MHRD caused maternal toxicity resulting in miscarriages and significant increase in incidence of foetuses with a skeletal variation (cervical rib). The skeletal variations were reabsorbed during the growing process of adjacent cervical vertebra. A dose providing exposure equivalent to 6-times the human exposure based on $AUC_{0\text{-}24hr}$ in rabbits was without adverse effects.

The pre- and postnatal study in rats did not show drug-related adverse findings in dams and pups up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous (E551)
Hypromellose (E464)
Maltitol (E965)
Mannitol (E421)
Povidone (K25) (E1201)
Sodium chloride
Strawberry flavour (including propylene glycol)
Sucralose (E955)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

After reconstituition, use within 10 hours.

6.4 Special precautions for storage

Before reconstitution: This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

After reconstitution: Do not store above 30°C.

6.5 Nature and contents of container

Amber glass bottle with a tamper-evident child-resistant screw cap.

Each carton contains: 1 bottle, 1 press-in bottle adapter, 1 measuring cup, a 3 mL oral syringe with orange plunger and a 10 mL oral syringe with transparent plunger.

6.6 Special precautions for disposal

Do not shake the bottle.
Avoid skin contact.

It is recommended that Xofluza granules for oral suspension should be re constituted by a healthcare professional prior to dispensing. If necessary, the patient or caregiver may also reconstitute the oral suspension. The healthcare professional must counsel the individual or caregiver on how to reconstitute the suspension and must advise them to read the instructions for use before preparing and administering.

Xofluza granules for oral suspension should be taken immediately or within 10 hours of reconstitution. Discard the suspension if not used within 10 hours of reconstitution.

Preparation of oral suspension

1 Gently tap the bottom of the bottle to loosen the granules.
2 Add a measured 20 mL of drinking water to the granules, using a measuring cup.
3 Do not shake the bottle.
4 Gently swirl the suspension to ensure that the granules are evenly suspended.
5 Write the 'Discard after' time (10 hours from reconstitution time) on the bottle label.
6 Indicate the volume of oral suspension (2 mg/mL) to withdraw, based on body weight (see Table 1).

The appearance after reconstitution is a greyish white, white to light yellow opaque suspension.

Refer to the Instructions for Use included within the carton for full details on preparation and administration of Xofluza granules for oral suspension. Check the manufacturer's instructions for the size and dimensions of the enteral feeding tube.

For administration through enteral feeding tubes, draw up suspension with an enteral syringe. Flush with1 mL of water before and after enteral administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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