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TAB-XOF-2023 05-0

Xofluza®

baloxavir marboxil

1. DESCRIPTION

1.1 THERAPEUTIC/ PHARMACOLOGIC CLASS OF DRUG

ATC Code: J05AX25

1.2 TYPE OF DOSAGE FORM

Tablets

Xofluza 20 mg tablets are white to light yellow, oblong shaped film-coated tablets debossed with "Ⓢ772" on one side and "20" on the other side.
Xofluza 40 mg tablets are white to light yellow, oblong shaped film-coated tablets debossed on one side with "BXM40".

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: baloxavir marboxil
20 mg film-coated tablets containing 20 mg baloxavir marboxil
40 mg film-coated tablets containing 40 mg baloxavir marboxil

Excipients: Lactose monohydrate, croscarmellose sodium, povidone, microcrystalline cellulose, sodium stearyl fumarate, hypromellose, talc, titanium dioxide.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Treatment of Influenza

Xofluza is indicated for the treatment of acute uncomplicated influenza in patients aged 12 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

(see section 3.1.2 Clinical/ Efficacy Studies).

Prophylaxis of Influenza

Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 12 and above.

Limitations of Use

Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use Xofluza (see section 3.1.2 Clinical/Efficacy Studies, Resistance Monitoring during Clinical Development).

2.2 DOSAGE AND ADMINISTRATION

General

Xofluza may be taken with or without food (see section 3.2 Pharmacokinetic Properties).

Treatment of Influenza

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

Prophylaxis of Influenza

A single dose of Xofluza should be taken within 48 hours following close contact with a symptomatic individual.

Dosage

Treatment or Post-Exposure Prophylaxis of Adults and Adolescents (≥12 years of age)

The recommended dose of Xofluza depending on body weight is shown in Table 1.

Table 1 Xofluza dosing by patient weight

Patient Body Weight (kg)	Recommended Single Oral Dose
40 kg to < 80 kg	40 mg
≥ 80 kg	80 mg

Dose Modifications

No dose reductions of Xofluza are recommended.

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Xofluza in patients < 12 years of age has not been established. For patients ≥ 12 years see 2.2 Dosage and Administration.

Geriatric use

No dosage adjustment is recommended (see section 3.2.5 Pharmacokinetics in Special Populations, Geriatric Population).

Renal Impairment

The safety and efficacy of Xofluza has not been studied in patients with renal impairment. A change in dose is not required for patients with renal impairment (see section 3.2.5 Pharmacokinetics in Special Populations, Renal impairment).

Hepatic Impairment

No dose adjustment is required in patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment (see section 3.2.5 Pharmacokinetics in Special Populations, Hepatic impairment). Xofluza has not been studied in patients with severe hepatic impairment.

2.3 CONTRAINDICATIONS

Xofluza is contraindicated in patients with a known hypersensitivity to baloxavir marboxil or any of the excipients (see section 2.6.2 Postmarketing Experience).

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

No warnings and precautions based on the available data.

2.4.2 Drug Abuse and Dependence

Not applicable

2.4.3 Ability to Drive and Use Machines

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

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility

No effects on fertility were observed in animal studies performed with baloxavir marboxil (see section 3.3.3 Impairment of Fertility).

2.5.2 Pregnancy

There are no adequate and well-controlled studies with Xofluza in pregnant women. The potential risk of Xofluza in pregnant women is unknown. Xofluza should be avoided during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Baloxavir marboxil did not cause malformations in rats or rabbits. High dose levels of baloxavir marboxil given to pregnant rabbits caused maternal toxicity resulting in miscarriages and an increase in the incidence rates of minor skeletal abnormalities in rabbits but no malformations. Such effects were not seen in rats (see section 3.3.4 Reproductive toxicity).

Labor and Delivery

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

2.5.3 Lactation

It is not known whether baloxavir marboxil and the active metabolite, baloxavir, are excreted in human breast milk. When dosed at 1 mg/kg baloxavir marboxil or its metabolites are secreted in the milk of lactating rats.

Therefore, a decision should be made whether to discontinue nursing or to initiate treatment with Xofluza, taking into consideration the potential benefit of Xofluza to the nursing mother and the potential risk to the infant.

2.5.4 Pediatric Use

The safety and efficacy in pediatric patients (< 12 years of age) has not been established.

2.5.5 Geriatric Use

The safety and efficacy of Xofluza for the treatment of influenza in geriatric patients age ≥ 65 years and weighing at least 40 kg have been established. See sections 2.2.1 Special Dosage Instructions, 2.6.1 Clinical Trials and 3.2.5 Pharmacokinetics in Special Populations.

2.5.6 Renal Impairment

The safety and efficacy of Xofluza in patients with renal impairment has not been studied. See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.5.7 Hepatic Impairment

The safety and efficacy of Xofluza in patients with severe hepatic impairment has not been studied. See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

The overall safety profile of Xofluza is based on data from 2483 subjects in 18 clinical trials receiving Xofluza.

Treatment of Influenza

No adverse drug reactions have been identified based on pooled data from 3 placebo-controlled clinical studies (Studies 1518T0821, 1601T0831 and 1602T0832) in adult and adolescent patients, in which a total of 1640 patients have received Xofluza. This includes otherwise healthy adults, and adolescents and patients at high risk of developing complications associated with influenza, e.g. elderly patients and patients with chronic cardiac or respiratory disease. 1334 patients (81.3%) were adults ≥ 18 years to ≤ 64 years, 209 patients (12.7%) were adults ≥ 65 years and 97 patients (5.9%) were adolescents (≥ 12 years to < 18 years). Of these, 1440 patients received Xofluza at 40 mg and 80 mg doses and 100 patients each received 10 mg or 20 mg doses. The safety profile in patients at high risk was similar to that in otherwise healthy adults and adolescents.

Prophylaxis of Influenza

No adverse drug reactions have been identified based on a placebo-controlled clinical study (study 1719T0834), in which a total of 374 subjects received Xofluza. The safety profile of Xofluza administered for post-exposure prophylaxis of influenza is comparable to the safety profile established for the treatment of influenza.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Xofluza (Table 2) based on spontaneous case reports and cases from non-interventional study programs. 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).

Bloody stool, epistaxis, haematuria, metrorrhagia etc. have been reported. Current evidence suggests that influenza is the most likely cause of the bleeding/haemorrhage reported.

Table 2 Adverse drug reactions from postmarketing experience

Adverse reactions	Frequency Category
Immune system disorders	
Anaphylaxis	Unknown[1]
Anaphylactic reactions	Unknown[1]
Hypersensitivity	Unknown[1]
Skin and subcutaneous disorders	
Urticaria	Uncommon[2]
Angioedema	Unknown[1]

[1] Not observed in clinical trials. As these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.
[2] Calculated from frequency of events in completed clinical studies.

Description of selected adverse drug reactions from postmarketing experience

Hypersensitivity reactions have been observed in the postmarketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including urticaria and angioedema.

2.7 OVERDOSE

Clinical experience

Reports of overdoses with Xofluza have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported. Whilst a limited number of cases of overdose have been reported in association with adverse events, 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.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Effects of Other Drugs on Baloxavir Marboxil or its Active Metabolite Baloxavir

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

Effects of Baloxavir Marboxil or its Active Metabolite Baloxavir on Other Drugs

In *in vitro* studies at clinically relevant concentrations, baloxavir marboxil and its active metabolite, baloxavir did not inhibit any of the following isozymes of CYP or UGT family: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 isozymes). In *in vitro* studies at clinically relevant concentrations, baloxavir marboxil and baloxavir did not cause significant induction of CYP1A2, CYP2B6, and CYP3A4 . In *in vitro* transporter studies at clinically relevant concentrations, baloxavir marboxil and baloxavir inhibited the efflux transporter (P-gp). 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, hence no relevant pharmacokinetic interaction is anticipated between baloxavir and medicines which are substrates of these transporters.

A single 40 mg dose of baloxavir marboxil did not affect the pharmacokinetics of midazolam, a substrate of CYP3A4, suggesting that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of CYP3A.

A single 80 mg dose of baloxavir marboxil did not affect the pharmacokinetics of digoxin, a substrate of P-gp, suggesting that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of P-gp.

A single 80 mg dose of baloxavir marboxil decreased C_{max} and $AUC_{0\text{-}inf}$ of rosuvastatin, a substrate of BCRP, by 18% and 17%, respectively. These decreases are not considered to be clinically meaningful and indicate that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of BCRP.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

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

Nonclinical 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 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 titer 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.

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

At twice the expected exposure from recommended dosing, Xofluza did not prolong the QTc interval.

3.1.2 Clinical / Efficacy Studies

Treatment of Influenza
Otherwise healthy patients
Study 1601T0831

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

A total of 1436 patients were randomized to receive treatment in the 2016 - 2017 Northern Hemisphere influenza season. Patients were randomized to receive 40 mg or 80 mg of Xofluza according to weight (< 80 kg or ≥ 80kg respectively), 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%). 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). A statistically significant and clinically meaningful improvement in the

primary endpoint was seen for Xofluza when compared with placebo, see Table 3.

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

Time to Alleviation of Symptoms (Median [hours])			
Xofluza 40/80 mg (95% CI) N=455	**Placebo (95% CI) N=230**	**Difference between Xofluza and placebo (95% CI for difference)**	**P-value**
53.7 (49.5, 58.5)	80.2 (72.6, 87.1)	-26.5 (−35.8, −17.8)	<0.0001

CI: Confidence interval

When the Xofluza group was compared to the oseltamivir group, there was no statistically significant difference in time to alleviation of symptoms (53.5 h vs 53.8 h respectively), see Table 4.

Table 4 Time to Alleviation of Symptoms in Otherwise Healthy Patients with Influenza (≥ 20 years of age), (Xofluza vs Oseltamivir)

Time to Alleviation of Symptoms (Median [hours])			
Xofluza 40/80 mg (95% CI) N=375	**Oseltamivir (95% CI) N=377**	**Difference between Xofluza and Oseltamivir (95% CI for difference)**	**P-value**
53.5 (48.0, 58.5)	53.8 (50.2, 56.4)	-0.3 (−6.6, 6.6)	0.7560

CI: Confidence interval

Secondary endpoints included time to resolution of fever and culture-based assessment of time to cessation of viral shedding (by virus titer).

Resolution of Fever
Following study drug administration there was faster resolution of fever in the Xofluza group compared with the placebo group. The median time to resolution of fever in patients treated with Xofluza 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 Xofluza group compared with the oseltamivir group.

Antiviral Activity
Patients treated with Xofluza showed a rapid reduction in virus titer. The median time to cessation of viral shedding determined by virus titer was 24.0 hours (95% CI: 24.0, 48.0) in the Xofluza group compared with 72.0 hours (95% CI: 72.0, 96.0) in the oseltamivir group and 96.0 hours (95% CI: 96.0, 96.0) in the placebo group.

Study 1518T0821
The phase 2 study was designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo in otherwise healthy adult patients (aged ≥ 20 years to ≤ 64 years) with influenza. A total of 400 patients were randomized to one of three dose groups of Xofluza (10, 20 or 40 mg) or placebo in the 2015-2016 Northern Hemisphere influenza season in Japan. The predominant influenza virus strain was A/H1N1pdm subtype (61% to 71%) followed by B subtype (21% to 24%) and A/H3N2 subtype (5% to 13%).

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

Resolution of Fever
The median time to resolution of fever was significantly reduced in all dose groups compared with placebo. At 40 mg the median time was 28.9 hours (95% CI: 24.5, 34.7) versus 45.3 hours (95% CI: 35.6, 54.0) in the placebo group. Viral endpoint results were consistent with those in study 1601T0831.

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

A total of 2184 patients were randomized to receive a single oral dose of 40 mg or 80 mg of Xofluza according to 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 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). A statistically significant improvement in the primary endpoint was observed for Xofluza when compared with placebo, see Table 5.

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

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

When the Xofluza group was compared to the oseltamivir group, there was no statistically significant difference in time to improvement of influenza symptoms (73.2 h vs 81.0 h respectively), see Table 6.

Table 6 Time to Improvement of Influenza Symptoms (Xofluza vs Oseltamivir)

Time to Improvement of Influenza Symptoms (Median [hours])			
Xofluza 40/80 mg (95% CI) N=385	**Oseltamivir (95% CI) N=388**	**Difference between Xofluza and Oseltamivir (95% CI for difference)**	**P-value**
73.2 (67.5, 85.1)	81.0 (69.4, 91.5)	-7.7 (−22.7, 7.9)	0.8347

Virus Subtype
For patients infected with type A/H3 virus (predominant strain), the median time to improvement of influenza symptoms was shorter in the Xofluza group compared with the placebo group but not when compared with the oseltamivir group (see Table 7). In the subgroup of patients infected with type B virus, the median time to improvement of influenza symptoms was shorter in the Xofluza group compared with both the placebo and oseltamivir group.

Table 7 Time to Improvement of Symptoms by Influenza Virus Subtype

Time to Improvement of Symptoms (Hours) Median [95% CI]			
Virus	**Xofluza**	**Placebo**	**Oseltamivir**
A/H3	75.4 [62.4, 91.6] N= 180	100.4 [88.4, 113.4] N= 185	68.2 [53.9, 81.0] N= 190
B	74.6 [67.4, 90.2] N= 166	100.6 [82.8, 115.8] N= 167	101.6 [90.5, 114.9] N= 148

Resolution of Fever
The proportion of patients who had fever was reduced more rapidly in the Xofluza group than in the placebo group following study drug administration. The median time to resolution of fever was 30.8 hours (95% CI: 28.2, 35.4) in the Xofluza group compared with 50.7 hours (95% CI: 44.6, 58.8) in the placebo group. No clear differences between the Xofluza group and the oseltamivir group were observed.

Incidence of Influenza-Related Complications
The overall incidence of influenza-related complications (death, hospitalization, sinusitis, otitis media, bronchitis, and/or pneumonia) was 2.8% (11/388 patients) in the Xofluza group compared with 10.4% (40/386 patients) in the placebo group and 4.6% (18/389 patients) in the oseltamivir 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).

The proportion of patients requiring systemic antibiotics for infections secondary to influenza infection was lower in the Xofluza group (3.4%) compared with the placebo group (7.5%), and the difference between these 2 groups was statistically significant ($p = 0.0112$). The proportion of patients requiring systemic antibiotics in the Xofluza group was comparable with the proportion in the oseltamivir group (3.9%).

Antiviral Activity
Patients at high risk of influenza complications, treated with Xofluza, showed a rapid reduction in virus titer and a significantly shortened time to cessation of viral shedding. The median time to cessation of viral shedding determined by virus titer was 48 hours in the Xofluza group compared with 96 hours in the placebo group and the oseltamivir group.

Prophylaxis of Influenza
Study 1719T0834
Study 1719T0834 was a phase 3, randomized, double-blind, multicenter, placebo-controlled study designed 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. Influenza-infected index patients were required to have onset of symptoms for ≤ 48 hours and subjects were required to have lived with the influenza-infected index patients for ≥ 48 hours.

A total of 749 subjects were randomized and received a single oral dose of Xofluza, according to body weight and age, or placebo, on Day 1. Subjects 12 years of age and over received 40 mg or 80 mg of Xofluza according to weight (40 to < 80 kg or ≥ 80 kg respectively). Subjects under 12 years of age were dosed according to body weight. The predominant influenza virus strains in the index patients of this study were the A/H3NX subtype (48.4% to 48.8%) and the A/H1N1pdm subtype (47.1% to 48.0%) followed by the B subtype (0.5% to 0.8%) according to household contact groups baloxavir marboxil and placebo, respectively. 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. Influenza virus positivity was assessed by reverse transcription polymerase chain reaction (RT-PCR), fever was defined as a body temperature (axillary) ≥ 37.5°C, and respiratory symptoms were defined as having a symptom of 'cough' or 'nasal discharge/nasal congestion' with a severity of '2, Moderate' or '3, Severe' as assessed in the subject diary.

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 (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**	**Risk Ratio (95% CI for risk ratio)**	**P-value**
1.9 (0.8, 3.8)	13.6 (10.3, 17.5)	0.14 (0.06, 0.30)	< 0.0001

Secondary endpoints
The proportion of asymptomatic influenza-infected (RT-PCR positive) subjects from Day 1 to Day 10 in the mITT population was similar between the treatment groups; 7.8% (29/374 subjects) in the baloxavir marboxil group and 7.7% (29/375 subjects) in the placebo group (adjusted risk ratio: 1.0 [95% CI: 0.61, 1.64], $p = 0.9917$).

The analysis for the secondary endpoint of proportion of subjects with influenza virus infection (RT-PCR positive regardless of clinical symptoms) in the period from Day 1 to Day 10 demonstrated results consistent with the primary endpoint. There was a reduction in the proportion of subjects with influenza virus infection from 30.4% (95% CI: 25.8, 35.3) in the placebo group to 13.1% (95% CI: 9.9, 16.9) in the baloxavir marboxil group.

Prophylaxis of Influenza in subjects ≥ 12 years
A total of 607 subjects 12 years of age and above were randomized and received a single oral dose of Xofluza, according to body weight and age, or placebo, on Day 1. The subgroup analysis of the primary endpoint by age revealed the proportion of symptomatic influenza-infected (RT-PCR positive) subjects from Day 1 to Day 10 was lower in the baloxavir marboxil group than in the placebo group for subjects 12 years of age and older (1.3% vs. 13.2%, $p < 0.0001$).

Resistance Monitoring during Clinical Development
Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir have been detected by serial passage of virus in cell culture in the presence of increasing concentrations of baloxavir. Reduced susceptibility of influenza A virus to baloxavir was observed in amino acid substitutions I38T (H1N1 and H3N2) and E199G (H3N2) in the polymerase acidic (PA) protein of the viral RNA polymerase complex. Influenza B virus isolates with reduced susceptibility to baloxavir have not been detected in cell culture.

Clinical studies: Influenza A virus isolates with treatment-emergent amino acid substitutions in the PA protein at position I38T/F/M/N/S associated with > 10 fold reduced susceptibility to baloxavir and influenza B virus isolates with treatment-emergent amino acid substitutions in the PA protein at position I38T associated with > 5 fold reduced susceptibility to baloxavir were observed in clinical studies. In addition, the E23K substitution, associated with a 5-fold reduced susceptibility to baloxavir, was observed in some influenza A virus isolates. The clinical impact of this reduced susceptibility is unknown.

No pre-treatment isolates, with amino acid substitutions associated with reduced susceptibility to baloxavir, were found in the clinical studies. Prescribers should consider available information from the CDC on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use Xofluza.

In the phase 3 study in otherwise healthy patients (1601T0831), PA/I38T/M were detected in 36 of 370 patients (9.7%) in the Xofluza treatment group. In the phase 3 study in high risk patients (1602T0832), PA/I38T/M/N were detected in 15 of 290 patients (5.2%) in the Xofluza treatment group.

In the phase 3 study of post-exposure prophylaxis treatment-emergent mutations 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.

Cross Resistance
No single amino acid substitution has been identified that could confer cross-resistance between baloxavir and neuraminidase inhibitors (e.g., peramivir, oseltamivir, zanamivir). However, a virus may carry amino acid substitutions associated with reduced susceptibility to baloxavir in the PA protein and to neuraminidase inhibitors in the neuraminidase and may therefore exhibit reduced susceptibility to both classes of inhibitors. The clinical relevance of phenotypic cross resistance evaluations has not been established.

3.1.3 Immunogenicity
Immune Response
Interaction studies with influenza vaccines and baloxavir marboxil have not been conducted. In studies of naturally acquired and experimental influenza, treatment with Xofluza did not impair normal humoral antibody response to infection.

3.2 PHARMACOKINETIC PROPERTIES
After oral administration, baloxavir marboxil is extensively converted to 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 of baloxavir in Japanese healthy adult subjects after a single oral administration of 40 mg baloxavir marboxil in the fasted and fed states are summarized in Table 9. The pharmacokinetic parameters of baloxavir in Caucasian healthy adult subjects after a single oral administration of 80 mg baloxavir marboxil in the fasted state are summarized in Table 10.

Table 9 Pharmacokinetic Parameters of Plasma baloxavir in Japanese healthy subjects after Administration of a Single Oral Dose of 40 mg of baloxavir marboxil in the Fasted and Fed State

Parameters	Geometric Mean (CV%)	
	Fasted	**Fed**
N	14	14
C_{max} (ng/mL)	130 (24.1)	67.6 (40.0)
T_{max}[a] (hr)	4.00 (3.00, 5.00)	4.00 (0.50, 5.00)
$AUC_{0\text{-}last}$ (ng·hr/mL)	6932 (19.2)	4406 (38.8)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7086 (19.6)	4540 (39.1)
$t_{1/2,z}$ (hr)	93.9 (21.6)	97.5 (22.8)
CL/F (L/hr)	4.78 (19.6)	7.45 (39.1)
V_z/F (L)	647 (19.1)	1050 (35.6)

[a] Median (Min, Max)

Table 10 Pharmacokinetic Parameters of Plasma Baloxavir in Caucasian healthy subjects after Administration of a Single Oral Dose of 80 mg of Baloxavir Marboxil in the Fasted State (Study 1612T081C)

Parameters	Geometric Mean (CV%)
N	12
C_{max} (ng/mL)	145 (25.4)
$AUC_{0\text{-}last}$ (ng·hr/mL)	6305 (21.2)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6551 (22.5)
$t_{1/2,z}$ (hr)	79.1 (22.4)
CL/F (L/hr)	10.3 (22.5)

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

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

3.2.2 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 following a single oral administration of 80 mg of baloxavir marboxil is approximately 1180 liters in Caucasian patients and 647 liters in Japanese subjects.

3.2.3 Metabolism
In vitro studies revealed that arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and the liver mainly contributes to the conversion from baloxavir marboxil to baloxavir and baloxavir is primarily metabolized by UGT1A3 with minor contribution from CYP3A4.

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

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

3.2.4 Elimination
The apparent terminal elimination half-life ($t_{1/2,z}$) of 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 9 and 10.

Linearity/non-linearity
Following single oral administration of baloxavir marboxil, baloxavir exhibits linear pharmacokinetics in the fasted state within the dose range of 6 mg to 80 mg.

3.2.5 Pharmacokinetics in Special Populations
Body weight
Body weight is identified as the significant covariate based on the population pharmacokinetic analysis. The dose proposed in adults is 40 mg for patients with body weight 40 kg to < 80 kg, and 80 mg for patients with body weight ≥ 80 kg.

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 a covariate on 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 with baloxavir marboxil for subjects aged 12 to 64 years did not identify a clinically meaningful effect of age on the pharmacokinetics of baloxavir.

Pediatric Population
The pharmacokinetics of Xofluza in pediatric patients (< 12 years of age) has not been established.

Geriatric Population
Pharmacokinetic data collected in patients ≥ 65 years show that drug exposure to baloxavir was similar to patients aged ≥ 12 to 64 years.

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. 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.

Hepatic impairment
Geometric mean ratios (90% confidence interval) of C_{max} and AUC of baloxavir in patients with moderate hepatic impairment (Child-Pugh class B) compared to healthy controls were 0.80 (0.50 – 1.28) and 1.12 (0.78 – 1.61), respectively. Since no clinically meaningful differences in the pharmacokinetics of baloxavir were observed 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 in patients with severe hepatic impairment has not been evaluated.

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

3.3.1 Carcinogenicity
Carcinogenicity studies have not been performed with baloxavir marboxil.

3.3.2 Genotoxicity
The pro-drug baloxavir marboxil, and its active form, baloxavir, were negative in bacterial reverse mutation tests, micronucleus tests with cultured mammalian cells, and baloxavir marboxil was negative in an *in vivo* rodent micronucleus test.

3.3.3 Impairment of Fertility
Baloxavir marboxil had no effects on fertility when given orally to male and female rats at doses up to 1000 mg/kg/day, which is equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

3.3.4 Reproductive toxicity
Baloxavir marboxil did not cause malformations in rats or rabbits. The oral embryo-fetal development study of baloxavir marboxil in rats with daily doses from gestation day 6 to 17 revealed no signs of maternal or fetal toxicity up to the highest tested dose of 1000 mg/kg/day, which is equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

In rabbits, a dose level of 1000 mg/kg/day (equivalent to 12-times the human exposure based on $AUC_{0\text{-}24hr}$ following the MHRD) caused maternal toxicity resulting in 2 miscarriages out of 19 and an increased incidence of fetuses with a skeletal variation (cervical rib), but no malformations. This minor skeletal variation is reabsorbed during the growing process of adjacent cervical vertebra. A dose of 100 mg/kg/day (equivalent to 7-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 of 1000 mg/kg/day, which is equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

3.3.5 Other
Not applicable

4. PHARMACEUTICAL PARTICULARS
4.1 STORAGE
Storage
Do not store above 30°C, store in the original package in order to protect from moisture.

Shelf life
As registered locally

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
The release of pharmaceuticals in the environment should be minimized. 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.

4.3 PACKS
2 x 20 mg tablets per blister card in secondary packaging
4 x 20 mg tablets per blister card in secondary packaging
1 x 40 mg tablets per blister card in secondary packaging
2 x 40 mg tablets per blister card in secondary packaging

Medicine: keep out of reach of children

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