XOFLUZA®

Baloxavir Marboxil

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Treatment of Influenza

XOFLUZA is indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and who are:

- otherwise healthy, or
- at high risk of developing influenza-related complications *[see Clinical Studies (13.2)]*.

1.2 Post-Exposure Prophylaxis of Influenza

XOFLUZA is indicated for post-exposure prophylaxis of influenza in persons 12 years of age and older following contact with an individual who has influenza [see Clinical Studies (13.3)].

1.3 Limitations of Use

Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use XOFLUZA *[see Microbiology (11.4) and Clinical Studies (13)]*.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

Initiate treatment with XOFLUZA

XOFLUZA should be taken as soon as possible after influenza symptom onset or exposure to influenza and may be taken with or without food. However, coadministration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided *[see Drug Interactions (7.1) and Clinical Pharmacology (11.3)]*.

2.2 Recommended Dosage

Treatment of Acute Uncomplicated Influenza or Post-Exposure Prophylaxis in Adults and Adolescents (12 Years of Age and Older)

XOFLUZA should be taken as a single dose as soon as possible and within 48 hours of influenza symptom onset for treatment of acute uncomplicated influenza or following contact with an individual who has influenza.

The recommended dosageof XOFLUZA in patients 12 years of age or older is a single weight-based dose displayed in Table 1.

Table 1 Recommended XOFLUZA Dosage in Adults and Adolescents (12 Years of Age and Older)

Patient Body Weight (kg)	Recommended Single Oral Dose
40 kg to less than 80 kg	Single dose of 40 mg
At least 80 kg	Single dose of 80 mg

3. DOSAGE FORMS AND STRENGTHS

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 with "BXM40" on one side.

4. CONTRAINDICATIONS

XOFLUZA is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. Serious allergic reactions have included anaphylaxis, angioedema, urticaria and erythema multiforme [*see Warnings and Precautions (5.1*)].

5. WARNINGS AND PRECAUTIONS

5.1. Hypersensitivity

Cases of anaphylaxis, urticaria, angioedema, and erythema multiforme have been reported in postmarketing experience with XOFLUZA. Appropriate treatment should be instituted if an allergic-like reaction occurs or is suspected. The use of XOFLUZA is contraindicated in patients with known hypersensitivity to XOFLUZA [*see Contraindications (4) and Adverse Reactions (6.2)].*

5.2. Risk of Bacterial Infections

There is no evidence of efficacy of XOFLUZA in any illness caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms, may coexist with, or occur as a complication of influenza. XOFLUZA has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety profile of XOFLUZA is based on data from 1,943 subjects 12 years of age and older in 4 controlled clinical trials who received XOFLUZA *[see Clinical Studies (13)]*.

Treatment of Acute Uncomplicated Influenza

The safety of XOFLUZA in adult and adolescent subjects is based on data from 3 placebo-controlled trials in which a total of 1,640 subjects received XOFLUZA: 1,334 subjects (81%) were 18 to 64 years of age, 209 subjects (13%) were adults 65 years of age or older and 97 subjects (6%) were adolescents 12 to 17 years of age. These trials included otherwise healthy adults and adolescents (N=910) and subjects at high risk of developing complications associated with influenza (N=730). Of these, 1,440 subjects received XOFLUZA at the recommended dose [*see Clinical Studies (13*)].

Table 2 displays the most common adverse events (regardless of causality assessment) reported in at least 1% of adult and adolescent subjects who received XOFLUZA at the recommended dose in Trials 1, 2 and 3.

Table 2 Incidence of Adverse Events Occurring in At Least 1% of Subjects Receiving XOFLUZA in the Acute Uncomplicated Influenza Trials 1, 2 and 3

Adverse Event	XOFLUZA (N= 1,440)	Placebo (N= 1,136)
Diarrhea	3%	4%
Bronchitis	3%	4%
Nausea	2%	3%
Sinusitis	2%	3%
Headache	1%	1%

Post-Exposure Prophylaxis of Influenza

The safety of XOFLUZA in adult and adolescent subjects is based on data from one placebo-controlled clinical trial in which 374 subjects, of which 303 were adult and adolescent subjects ≥ 12 years, received XOFLUZA: eight (3%) subjects were adults 65 years of age or older, and 12 (4%) subjects were adolescents 12 to 17 years of age. The most frequently reported AE in the total study population was nasopharyngitis which occurred in 6% of subjects who received XOFLUZA and 7% on placebo [see Clinical Studies (13.3)].

6.2. Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of XOFLUZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to XOFLUZA exposure.

Immune System Disorders: Anaphylactic reactions, anaphylactic shock, anaphylactoid reactions, hypersensitivity reactions, angioedema (swelling of face, eyelids, tongue and lips)

Skin and Subcutaneous Tissue Disorders: Rash, urticaria, erythema multiforme

Gastrointestinal Disorders: Vomiting, hematochezia, melena, colitis

Psychiatric Disorders: Delirium, abnormal behavior, hallucinations

7. DRUG INTERACTIONS

7.1. Effect of Other Drugs on XOFLUZA

Co-administration with polyvalent cation-containing products may decrease plasma concentrations of baloxavir which may reduce XOFLUZA efficacy. Avoid co-administration of XOFLUZA with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).

7.2. Vaccines

The concurrent use of XOFLUZA with intranasal live attenuated influenza vaccine (LAIV) has not been evaluated. Concurrent administration of antiviral drugs may inhibit viral replication of LAIV and thereby decrease the

effectiveness of LAIV vaccination. Interactions between inactivated influenza vaccines and XOFLUZA have not been evaluated.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no adequate and well-controlled studies with on XOFLUZA in pregnant women to inform a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with influenza virus infection in pregnancy *[see Clinical Considerations].* In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits with oral administration of baloxavir marboxil at exposures approximately 5 (rats) and 7 (rabbits) times the systemic baloxavir exposure at the maximum recommended human dose (MRHD) [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal outcomes including maternal death, stillbirth, birth defects, preterm delivery, low birth weight and small for gestational age.

Data

Animal Data

Baloxavir marboxil was administered orally to pregnant rats (20, 200, or 1,000 mg/kg/day from gestation day 6 to 17) and rabbits (30, 100, or 1,000 mg/kg/day from gestation day 7 to 19). No adverse embryo-fetal effects were observed in rats up to the highest dose of baloxavir marboxil (1,000 mg/kg/day), resulting in systemic baloxavir exposure (AUC) of approximately 5 times the exposure at the MRHD. In rabbits, fetal skeletal variations occurred at a maternally toxic dose (1,000 mg/kg/day) resulting in 2 abortions out of 19 pregnancies. No adverse maternal or embryo-fetal effects were observed in rabbits at the middle dose (100 mg/kg/day) resulting in systemic baloxavir exposure (AUC) approximately 7 times the exposure at the MRHD.

In the prenatal and postnatal development study in rats, baloxavir marboxil was administered orally at 20, 200, or 1,000 mg/kg/day from gestation day 6 to postpartum/lactation day 20. No significant effects were observed in the offspring at maternal systemic baloxavir exposure (AUC) approximately 5 times the exposure at the MRHD.

8.2. Lactation

Risk Summary

There are no data on the presence of baloxavir marboxil in human milk, the effects on the breastfed infant, or the effects on milk production. Baloxavir and its related metabolites were present in the milk of lactating rats *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XOFLUZA and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Data

In a lactation study, baloxavir and its related metabolites were excreted in the milk of lactating rats administered baloxavir marboxil (1 mg/kg) on postpartum/lactation day 11, with peak milk concentration approximately 5 times that of maternal plasma concentrations occurring 2 hours post-dose. No effects of baloxavir marboxil on growth and postnatal development were observed in nursing pups at the highest oral dose tested in rats. Maternal systemic exposure was approximately 5 times the baloxavir exposure in humans at the MRHD.

8.3. Pediatric Use

The safety and effectiveness of XOFLUZA for the treatment of acute uncomplicated influenza have been established in pediatric patients 12 years of age and older weighing at least 40 kg *[see Adverse Reactions (6.1) and Clinical Studies (13)*]. The safety and effectiveness of XOFLUZA have not been established in pediatric patients less than 12 years of age.

Treatment of Acute Uncomplicated Influenza in Otherwise Healthy Pediatric Patients

The safety and effectiveness of XOFLUZA in otherwise healthy pediatric patients 12 years of age and older weighing at least 40 kg is supported by one randomized, double-blind, controlled trial (Trial 2) *[see Clinical Studies (13.1)]*. In this phase 3 trial, 117 adolescents 12-17 years old were randomized and received either XOFLUZA (N=76) or placebo (N=41). The median time to alleviation of symptoms in influenza-infected adolescent subjects aged 12 to 17 years was 54 hours and 93 hours for subjects who received XOFLUZA (N=63) or placebo (N=27),

respectively, and was comparable to that observed in the overall trial population *[see Clinical Studies (13.1)].* Adverse events reported in adolescents were similar to those reported in adults *[see Adverse Reactions (6.1)].*

Treatment of Acute Uncomplicated Influenza in Pediatric Patients at High Risk for Influenza Complications
The safety and effectiveness of XOFLUZA in pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk of developing influenza-related complications is supported by extrapolation from a clinical trial in otherwise healthy adults and adolescents with acute uncomplicated influenza (Trial 2), and from one randomized, double-blind, phase 3 controlled trial in patients at high risk for influenza complications (Trial 3) in which 38 adolescents aged 12 to 17 years were randomized and received either XOFLUZA (N=21) or placebo (N=17). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years who were infected with influenza was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively) *[see Clinical Studies (13.2)]*. Adverse events reported in adolescents were similar to those reported in adults *[see Adverse Reactions (6.1)].*

Post-Exposure Prophylaxis of Influenza in Pediatric Subjects
The safety and effectiveness of XOFLUZA for post-exposure prophylaxis in adolescents (12 years to < 18 years) is supported by one randomized, double-blind, controlled trial conducted in Japan (Trial 4) [*see Clinical Studies (13.3)*]. Subjects in this trial were randomized in a 1:1 ratio to receive XOFLUZA or placebo. A total of 12 subjects from ≥ 12 to < 18 years of age received XOFLUZA. The incidence of RT-PCR-confirmed symptomatic influenza was similar in the XOFLUZA and placebo arms in the limited number of adolescent subjects aged 12 to 17 years of age [*see Clinical Studies (13.3)*]. Adverse events reported in adolescent subjectswere similar to those reported in adults in the same trial [*see Adverse Reactions (6.1)*].

The safety and efficacy of XOFLUZA for post-exposure prophylaxis of influenza in pediatric subjects less than 12 years of age have not been established.

8.4. Geriatric Use
The safety and effectiveness of XOFLUZA in subjects 65 years of age and older has been established and is supported by one randomized, double-blind, controlled trial [*see Clinical Studies (13.2)].* In Trial 3, of 730 XOFLUZA-treated subjects at high risk of influenza-related complications, 209 (29%) subjects were 65 years of age and older. The median time to improvement of influenza symptoms in subjects 65 years of age and older was 70 hours in subjects who received XOFLUZA (N=112) and 88 hours in those who received placebo (N=102). The safety profile observed for this population was similar to that reported in the overall trial population except for nausea, which was reported in 6% of elderly subjects compared to 1% of subjects from 18 to 64 years of age.

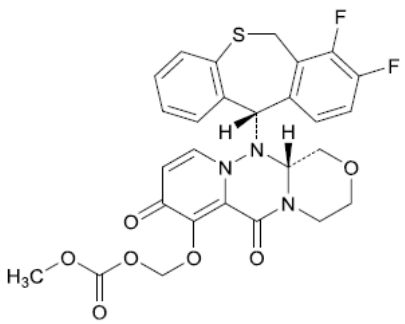
9. OVERDOSAGE
Treatment of an overdose of XOFLUZA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA.

Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding *[see Clinical Pharmacology (11.3)].*

10. DESCRIPTION
XOFLUZA (baloxavir marboxil) is an antiviral PA endonuclease inhibitor.

The active component of XOFLUZA is baloxavir marboxil.

The chemical name of baloxavir marboxil is ({(12aR)-12-[(11S)-7,8-Difluoro-6,11-dihydrodibenzo[b,e]thiepin11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methylmethyl carbonate. The empirical formula of baloxavir marboxil is $C_{27}H_{23}F_2N_3O_7S$ and the chemical structure is shown below.



Baloxavir marboxil has a molecular mass of 571.55 grams per mole and a partition coefficient (log P) of 2.26. It is freely soluble in dimethylsulfoxide, soluble in acetonitrile, slightly soluble in methanol and ethanol, and practically insoluble in water.

The inactive ingredients of XOFLUZA are: croscarmellose sodium, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, sodium stearyl fumarate, talc, and titanium dioxide.

11. CLINICAL PHARMACOLOGY

11.1. Mechanism of Action

Baloxavir marboxil is an antiviral drug with activity against influenza virus *[see Microbiology (11.4)]*.

11.2. Pharmacodynamics

Cardiac Electrophysiology

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

Exposure-Response Relationships

When XOFLUZA is dosed by weight, as recommended (40 mg in patients weighing 40-80 kg; and 80 mg in patients weighing at least 80 kg), no difference in baloxavir exposure-response (time to alleviation of influenza symptoms in the Otherwise Healthy population or time to improvement of influenza symptoms in the High Risk population) relationship has been observed.

11.3. Pharmacokinetics

Baloxavir marboxil is a prodrug that is almost completely converted to its active metabolite, baloxavir, following oral administration.

In Trial 2, at the recommended dose of 40 mg for subjects weighing less than 80 kg, the mean (CV%) values of baloxavir C_{max} and $AUC_{0\text{-}inf}$ were 96.4 ng/mL (45.9%) and 6160 ng·hr/mL (39.2%), respectively. At the recommended dose of 80 mg for subjects weighing 80 kg and more, the mean (CV%) values of baloxavir C_{max} and $AUC_{0\text{-}inf}$ were 107 ng/mL (47.2%) and 8009 ng·hr/mL (42.4%), respectively. Refer to Table 3 for pharmacokinetic parameters of baloxavir in healthy subjects. The pharmacokinetic profile of XOFLUZA was similar for adults and adolescents who were otherwise healthy and those at high risk of developing influenza-related complications.

Table 3 Pharmacokinetic Parameters of Plasma Baloxavir

Absorption	
T_{max} (hr)[a]	4
Effect of food (relative to fasting)[b]	C_{max}: ↓48%, $AUC_{0\text{-}inf}$: ↓36%
Distribution	
% Bound to human serum proteins[c]	92.9 -93.9
Ratio of blood cell to blood	48.5% -54.4%
Volume of distribution (V/F, L)[d]	1180 (20.8%)
Elimination	
Major route of elimination	Metabolism
Clearance (CL/F, L/hr)[d]	10.3 (22.5%)
$t^{1/2}$ (hr)[d,e]	79.1 (22.4%)
Metabolism	
Metabolic pathway[f]	UGT1A3, CYP3A4
Excretion	
% of dose excreted in urine[g]	14.7 (Total radioactivity), 3.3 (Baloxavir)
% of dose excreted in feces[g]	80.1 (Total radioactivity)

[a] Median
[b] Meal: approximately 400 to 500 kcal including 150 kcal from fat
[c] *in vitro*
[d] Geometric mean (geometric CV%)
[e] Apparent terminal elimination half-life
[f] Baloxavir is primarily metabolized by UGT1A3 with minor contribution from CYP3A4
[g] Ratio of radioactivity to radio-labeled [^{14}C]-baloxavir marboxil dose in mass balance study

Specific Populations

There were no clinically significant differences in the pharmacokinetics of baloxavir based on age (adolescents as compared to adults), or sex.

Patients with Renal Impairment
A population pharmacokinetic analysis did not identify a clinically meaningful effect of renal function on the pharmacokinetics of baloxavir in patients with creatinine clearance (CrCl) 50 mL/min and above. The effects of severe renal impairment on the pharmacokinetics of baloxavir marboxil or its active metabolite, baloxavir, have not been evaluated.

Patients with Hepatic Impairment
In a clinical study comparing pharmacokinetics of baloxavir in subjects with moderate hepatic impairment (Child-Pugh class B) to subjects with normal hepatic function, no clinically meaningful differences in the pharmacokinetics of baloxavir were observed.
The pharmacokinetics in patients with severe hepatic impairment have not been evaluated.

Body Weight
Body weight had a significant effect on the pharmacokinetics of baloxavir (as body weight increases, baloxavir exposure decreases). When dosed with the recommended weight-based dosing, no clinically significant difference in exposure was observed between body weight groups.

Race/Ethnicity
Based on a population pharmacokinetic analysis, baloxavir exposure is approximately 35% lower in non-Asians as compared to Asians; this difference is not considered clinically significant when the recommended dose was administered.

Drug Interaction Studies
Clinical Studies
No clinically significant changes in the pharmacokinetics of baloxavir marboxil and its active metabolite, baloxavir, were observed when co-administered with itraconazole (combined strong CYP3A and P-gp inhibitor), probenecid (UGT inhibitor), or oseltamivir.

No clinically significant changes in the pharmacokinetics of the following drugs were observed when coadministered with baloxavir marboxil: midazolam (CYP3A4 substrate), digoxin (P-gp substrate), rosuvastatin (BCRP substrate), or oseltamivir.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically
Cytochrome P450 (CYP) Enzymes: Baloxavir marboxil and its active metabolite, baloxavir, did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Baloxavir marboxil and its active metabolite, baloxavir, did not induce CYP1A2, CYP2B6, or CYP3A4.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes: Baloxavir marboxil and its active metabolite, baloxavir, did not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.

Transporter Systems: Both baloxavir marboxil and baloxavir are substrates of P-glycoprotein (P-gp). Baloxavir did not inhibit organic anion transporting polypeptides (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT) 1, OAT3, multidrug and toxin extrusion (MATE) 1, or MATE2K.

Potential for Interactions with Polyvalent Cations: Baloxavir may form a chelate with polyvalent cations such as calcium, aluminum, or magnesium in food or medications. A significant decrease in baloxavir exposure was observed when XOFLUZA was co-administered with calcium, aluminum, magnesium, or iron in monkeys. No study has been conducted in humans.

11.4. Microbiology
Mechanism of Action
Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication. The 50% inhibitory concentration (IC_{50}) values of baloxavir ranged from 1.4 to 3.1 nM (n=4) for influenza A viruses and 4.5 to 8.9 nM (n=3) for influenza B viruses in a PA endonuclease assay. Viruses with reduced susceptibility to baloxavir have amino acid substitutions in the PA protein.

Antiviral Activity
The antiviral activity of baloxavir against laboratory strains and clinical isolates of influenza A and B viruses was determined in an MDCK cell-based plaque reduction assay. The median 50% effective concentration (EC_{50}) values of baloxavir were 0.73 nM (n=31; range: 0.20-1.85 nM) for subtype A/H1N1 strains, 0.83 nM (n=33; range: 0.35-2.63 nM) for subtype A/H3N2 strains, and 5.97 nM (n=30; range: 2.67-14.23 nM) for type B strains. In an MDCK

cell-based virus titer reduction assay, the 90% effective concentration (EC_{90}) values of baloxavir against avian subtypes A/H5N1 and A/H7N9 were in the range of 0.80 to 3.16 nM. The relationship between antiviral activity in cell culture and clinical response to treatment in humans has not been established.

Resistance

Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir were selected 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 conferred by amino acid substitutions I38T (A/H1N1 and A/H3N2) and E199G (A/H3N2) in the PA protein of the viral RNA polymerase complex.

Clinical studies: Influenza A and B viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were observed in clinical studies (Table 4). The overall frequencies of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir in Trials 1, 2 and 3 *[see Clinical Studies (13)]* were 2.7% (5/182), 11% (39/370), and 5.5% (16/290), respectively. In Trial 4, of 374 subjects, including 71 subjects <12 years of age, who received XOFLUZA post-exposure prophylaxis, 49 were viral RNA-positive post-baseline, including 31 subjects who were evaluated for resistance. Of these 31 subjects, influenza virus with substitutions associated with reduced susceptibility to baloxavir was identified in 7/7 subjects who developed clinical influenza (as described for the primary endpoint) and 8/24 other subjects evaluated who did not meet the primary endpoint definition for clinical influenza [see Clinical Studies (14)]. Selection of influenza viruses with reduced susceptibility to baloxavir has occurred at higher frequencies in pediatric subjects, and such viruses were detected with overall frequencies of 20% (4/20), 27.9% (34/122), and 0% (0/21) in influenza A/H1N1, A/H3N2, and B virus infections, respectively, in pooled data from 3 pediatric treatment trials in subjects <12 years of age.

Table 4 Treatment-Emergent Amino Acid Substitutions in PA Associated with Reduced Susceptibility to Baloxavir

Influenza Type/ Subtype	**A/H1N1**	**A/H3N2**	**B**
Amino Acid Substitution	E23K/R, I38F/N/T	E23G/K, A37T, I38M/T, E199G	I38T

None of the treatment-emergent substitutions associated with reduced susceptibility to baloxavir were identified in virus from pre-treatment respiratory specimens in the clinical studies. Strains containing substitutions known to be associated with reduced susceptibility to baloxavir were identified in approximately 0.05% of PA sequences in the National Center for Biotechnology Information/GenBank database (queried August 2018).

Prescribers should consider currently available surveillance information on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use XOFLUZA.

Cross-Resistance

Cross-resistance between baloxavir and neuraminidase (NA) inhibitors, or between baloxavir and M2 proton pump inhibitors (adamantanes), is not expected, because these drugs target different viral proteins. Baloxavir is active against NA inhibitor-resistant strains, including A/H1N1 and A/H5N1 viruses with the NA substitution H275Y (A/H1N1 numbering), A/H3N2 virus with the NA substitutions E119V and R292K, A/H7N9 virus with the NA substitution R292K (A/H3N2 numbering), and type B virus with the NA substitutions R152K and D198E (A/H3N2 numbering). The NA inhibitor oseltamivir is active against viruses with reduced susceptibility to baloxavir, including A/H1N1 virus with PA substitutions E23K or I38F/T, A/H3N2 virus with PA substitutions E23G/K, A37T, I38M/T, or E199G, and type B virus with the PA substitution I38T. Influenza virus may carry amino acid substitutions in PA that reduce susceptibility to baloxavir and at the same time carry resistance-associated substitutions for NA inhibitors and M2 proton pump inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

Immune Response

Interaction studies with influenza vaccines and baloxavir marboxil have not been conducted.

12. NONCLINICAL TOXICOLOGY

12.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been performed with baloxavir marboxil.

Mutagenesis

Baloxavir marboxil and the active metabolite, baloxavir, were not mutagenic in *in vitro* and in *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, micronucleus tests with cultured mammalian cells, and in the rodent micronucleus assay.

Impairment of Fertility
In a fertility and early embryonic development study in rats, doses of baloxavir marboxil at 20, 200, or 1,000 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 7 of pregnancy. Males were dosed for 4 weeks before mating and throughout mating. There were no effects on fertility, mating performance, or early embryonic development at any dose level, resulting in systemic drug exposure (AUC) approximately 5 times the MRHD.

13. CLINICAL STUDIES

13.1 Treatment of Acute Uncomplicated Influenza – Otherwise Healthy Subjects

Adults and Adolescents (Aged 12 Years and Older)

Two randomized controlled double-blinded clinical trials conducted in two different influenza seasons evaluated efficacy and safety of XOFLUZA in otherwise healthy subjects with acute uncomplicated influenza.

In Trial 1, a placebo-controlled phase 2 dose-finding trial, a single oral dose of XOFLUZA was compared with placebo in 400 adult subjects 20 to 64 years of age in Japan. All subjects in Trial 1 were Asian, the majority of subjects were male (62%), and the mean age was 38 years. In this trial, among subjects who received XOFLUZA and had influenza virus typed, influenza A/H1N1 was the predominant strain (63%), followed by influenza B (25%), and influenza A/H3N2 (12%).

In Trial 2 (NCT02954354), a phase 3 active- and placebo-controlled trial, XOFLUZA was studied in 1,436 adults and adolescents with signs and symptoms of influenza in the U.S. and Japan. Subjects were 12 to 64 years of age and weighed at least 40 kg. Adults ages 20 to 64 years received weight-based XOFLUZA (subjects who weighed 40 to less than 80 kg received 40mg and subjects who weighed 80 kg and above received 80 mg) or placebo as a single oral dose on Day 1 or oseltamivir twice a day for 5 days. Subjects in the XOFLUZA and placebo arms received a placebo for the duration of oseltamivir dosing after XOFLUZA or placebo dosing in that arm. Adolescent subjects 12 to less than 20 years of age received weight-based XOFLUZA or placebo as a single oral dose.

Seventy-eight percent of subjects in Trial 2 were Asian, 17% were White, and 4% were Black or African American. The mean age was 34 years, and 11% of subjects were less than 20 years of age; 54% of subjects were male and 46% female. In Trial 2, 1,062 of 1,436 enrolled subjects had influenza confirmed by RT-PCR and were included in the efficacy analysis (XOFLUZA N=455, placebo N=230, or oseltamivir N=377). Among subjects who received XOFLUZA and had influenza virus typed, influenza A/H3N2 was the predominant strain (90%), followed by influenza B (9%), and influenza A/H1N1 (2%).

In both Trials 1 and 2, eligible subjects had an axillary temperature of at least 38˚C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptom onset. Subjects participating in the trial were required to self-assess their influenza symptoms as “none”, “mild”, “moderate” or “severe” twice daily. The primary efficacy population was defined as those with a positive rapid influenza diagnostic test (Trial 1) or positive influenza RT-PCR (Trial 2) at trial entry.

The primary endpoint of both trials, time to alleviation of symptoms, was defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the subject as none or mild for a duration of at least 21.5 hours.

In both trials, XOFLUZA treatment at the recommended dose resulted in a statistically significant shorter time to alleviation of symptoms compared with placebo in the primary efficacy population (Tables 5 and 6).

Table 5 Time to Alleviation of Symptoms after Single Dose in Otherwise Healthy Adults with Acute Uncomplicated Influenza in Trial 1 (Median Hours)

	XOFLUZA 40 mg (95% CI[a]) N = 100	**Placebo (95% CI[a]) N = 100**
Adults (20 to 64 Years of Age)	50 hours[b] (45, 64)	78 hours (68, 89)

[a]CI: Confidence interval
[b]XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Gehan-Breslow’s generalized Wilcoxon test (p-value: 0.014, adjusted for multiplicity using the Bonferroni method). The primary analysis using the Cox Proportional Hazards Model did not reach statistical significance (p-value: 0.165).

Table 6 Time to Alleviation of Symptoms after Single Dose in Otherwise Healthy Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 2 (Median Hours)

	XOFLUZA 40 mg or 80 mg (95% CI[a]) N = 455	Placebo (95% CI[a]) N = 230
Subjects (≥ 12 Years of Age)	54 hours[b] (50, 59)	80 hours (73, 87)

.
[a]CI: Confidence interval
[b]XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Peto-Prentice's generalized Wilcoxon test (p-value: <0.001).

In Trial 2, there was no difference in the time to alleviation of symptoms between subjects (age ≥ 20) who received XOFLUZA (54 hours) and those who received oseltamivir (54 hours). For adolescent subjects (12 to 17 years of age) in Trial 2, the median time to alleviation of symptoms for subjects infected with influenza and who received XOFLUZA (N=63) was 54 hours (95% CI of 43, 81) compared to 93 hours (95% CI of 64, 118) in the placebo arm (N=27).

The number of subjects who received XOFLUZA at the recommended dose and who were infected with influenza type B virus was limited, including 24 subjects in Trial 1 and 38 subjects in Trial 2. In the influenza B subset in Trial 1, the median time to alleviation of symptoms in subjects who received 40 mg XOFLUZA was 63 hours (95% CI of 43, 70) compared to 83 hours (95% CI of 58, 93) in subjects who received placebo. In the influenza B subset in Trial 2, the median time to alleviation of symptoms in subjects who received 40 mg or 80 mg XOFLUZA was 93 hours (95% CI of 53, 135) compared to 77 hours (95% CI of 47, 189) in subjects who received placebo.

13.2 Treatment of Acute Uncomplicated Influenza – High Risk Subjects

Trial 3 (NCT02949011) was a randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of a single oral dose of XOFLUZA compared with placebo or oseltamivir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza-related complications.

A total of 2,182 subjects with signs and symptoms of influenza were randomized to receive a single oral dose of 40 mg or 80 mg of XOFLUZA according to body weight (subjects who weighed 40 to less than 80 kg received 40 mg and subjects who weighed 80 kg and above received 80 mg) (N=729), oseltamivir 75 mg twice daily for 5 days (N=725), or placebo (N=728). Twenty-eight percent of subjects were Asian, 59% were White, and 10% were Black or African American. The mean age was 52 years, and 3% of subjects were less than 18 years of age; 43% of subjects were male and 57% female.

High risk factors were based on the Centers for Disease Control definition of health factors known to increase the risk of developing serious complications from influenza. The majority of subjects had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity, or were 65 years of age or older.

In Trial 3, 1,158 of the 2,182 enrolled subjects had influenza confirmed by RT-PCR and were included in the efficacy analysis (XOFLUZA N=385, placebo N=385, or oseltamivir N=388). Among subjects in whom only one type/subtype of influenza virus was identified, 50% were infected with subtype A/H3N2, 43% were infected with type B, and 7% were infected with subtype A/H1N1.

Eligible subjects had an axillary temperature of at least 38˚C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptom onset. Subjects participating in the trial were required to self-assess their influenza symptoms as "none", "mild", "moderate" or "severe" twice daily. A total of 215 subjects (19%) had pre-existing symptoms (cough, muscle or joint pain, or fatigue) associated with their underlying high-risk condition that were worsened due to influenza infection. 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). This endpoint included alleviation of new symptoms and improvement of any pre-existing symptoms that had worsened due to influenza. A statistically significant improvement in the primary endpoint was observed for XOFLUZA when compared with placebo, see Table 7.

Table 7 Time to Improvement of Symptoms After Single Dose in High Risk Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 3 (Median Hours)

XOFLUZA 40/80 mg (95% CI[a]) N=385	Placebo (95% CI[a]) N=385
73[b] (67, 85)	102[b] (93, 113)

[a]CI: Confidence Interval

[b]XOFLUZA treatment resulted in a significant reduction in Time to Improvement of Influenza Symptoms compared to placebo using Peto-Prentice's generalized Wilcoxon test (p-value: <0.001).

There was no statistically significant difference in the median time to improvement of influenza symptoms in the subjects who received XOFLUZA (73 hours) and those who received oseltamivir (81 hours). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years infected with influenza virus was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively).

For subjects infected with type B virus, the median time to improvement of influenza symptoms was 75 hours in the XOFLUZA group (95% CI of 67, 90) compared to 101 hours in the placebo group (95% CI of 83, 116).

13.3 Post-Exposure Prophylaxis of Influenza

Trial 4 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 were household contacts of influenza-infected patients in Japan. Influenza-infected index patients were required to have onset of symptoms for ≤ 48 hours, and subjects (household contacts) were required to have lived with the influenza-infected index patient for ≥ 48 hours.

A total of 607 subjects (XOFLUZA N=303, placebo N=304) ≥ 12 years of age were randomized and received a single oral dose of XOFLUZA according to body weight and age, or placebo, on day 1. Subjects received 40 mg or 80 mg of XOFLUZA according to body weight (40 to < 80 kg or ≥ 80 kg, 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 from day 1 to day 10. Influenza infection was confirmed by 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 moderate or severe as assessed by the subject.

The mean age of subjects that were ≥ 12 years of age in Trial 4 was 40 years; 33 (5%) were ≥ 12 to < 18 years of age, 551 (91%) were ≥ 18 to < 65 years of age, and 23 (4%) were ≥ 65 years of age. All subjects were Asian, 84% were female, and 16% were male. The predominant influenza virus strains in the index patients of this study were the A/H3N2 subtype (49%) and the A/H1N1 subtype (46%), followed by the B subtype (1%).

In subjects that were ≥12 years of age, there was a statistically significant reduction in the proportion of household contacts (subjects) with laboratory-confirmed clinical influenza from 13% in the placebo group to 1% in the XOFLUZA group (see Table 11).

Table 11 Proportion of Household Contacts (Subjects 12 Years of Age and Older) Infected with Influenza Virus with Fever and at Least One Respiratory Symptom (Trial 4)

XOFLUZA (95% CI[a]) N=303	**Placebo (95% CI[a]) N=304**
1% (0, 3)	13% (10, 17)

[a]CI: Confidence interval

XOFLUZA treatment resulted in a significant reduction in the risk ratio of patients who were infected with influenza virus and presented with fever compared to placebo using modified Poisson regression for a binary response (p-value: < 0.0001).

14. HOW SUPPLIED/STORAGE AND HANDLING

XOFLUZA Tablets:

How Supplied

- 20 mg white to light yellow, oblong shaped film-coated tablets debossed with "⑳772" on one side and "20" on the other side available as:
  - 4 x 20 mg tablets per blister card in secondary packaging

- 40 mg white to light yellow, oblong shaped film-coated tablets debossed with "BXM40" on one side available as:
  - 1 x 40 mg tablet per blister card in secondary packaging

Storage
Do not store above 30°C, store in the original package in order to protect from moisture.

15. PATIENT COUNSELING INFORMATION
Advise the patient to read the NPRA-approved Patient Information Leaflet (RiMUP).

Important Dosing Information
Instruct patients to begin treatment with XOFLUZA as soon as possible at the first appearance of influenza symptoms, within 48 hours of onset of symptoms. Instruct patients to start taking XOFLUZA for prevention as soon as possible after exposure *[see Dosage and Administration (2)]*.

XOFLUZA can be taken with or without food, but advise patients not to take with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) *[see Dosage and Administration (2) and Drug Interactions (7.1)]*.

Advise patients to follow the healthcare provider's dosing recommendation for a single, one-time dose of XOFLUZA. XOFLUZA is dosed based on weight and is available in blister card containing one tablet of 40 mg to be taken as a single 40 mg dose and blister card containing four tablets of 20 mg to be taken together as a single 80 mg dose [*see How Supplied/Storage and Handling (14)].*

Hypersensitivity
Advise patients and/or caregivers of the risk of severe allergic reactions such as anaphylaxis, angioedema, urticaria and erythema multiforme. Instruct patients and/or caregivers to seek immediate medical attention if an allergic-like reaction occurs or is suspected [*see Contraindications (4) and Warnings and Precautions (5.1)].*

Influenza Vaccines
Because of the potential for antivirals to decrease the effectiveness of live attenuated influenza vaccines, advise patients to consult their healthcare provider prior to receiving a live attenuated influenza vaccine after taking XOFLUZA *[see Drug Interactions (7.2)]*.

Medicine: keep out of reach of children

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