

XOFLUZA®



Baloxavir Marboxil

Film coated tablets

NAME OF THE MEDICINAL PRODUCT

XOFLUZA 40 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

XOFLUZA 40 mg film-coated tablets

Each tablet contains 40 mg baloxavir marboxil.

Excipients with known effect

Lactose Intolerance:

Each XOFLUZA 40 mg tablet contains 155.8 mg lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium:

Each XOFLUZA 40 mg tablet contains 2.26 mg sodium.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 11.

PHARMACEUTICAL FORM

Film-coated tablets

CLINICAL PARTICULARS

1 Therapeutic indications

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 .

1.2 Post-Exposure Prophylaxis of Influenza

Important note: the medical approach is that prevention by vaccination is better than prevention by antimicrobial agents.

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.

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 Warnings and Precautions (5.2), Microbiology (12.4) and Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

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 (12.3)]*.

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 dosage of XOFLUZA in patients 12 years of age or older is a single weight-based dose displayed in Table 1:

Table 1 Recommended XOFLUZA Tablet Dosage in Adults and Adolescents 12 Years of age and Older

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

3 DOSAGE FORMS AND STRENGTHS

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 [see Description (11)]. 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 or 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 (14)*].

Treatment of Acute Uncomplicated Influenza

Adult and Adolescent Subjects (≥ 12 Years of Age):

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 (81%) subjects were 18 to 64 years of age, 209 (13%) subjects were adults 65 years of age or older, and 97 (6%) subjects 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 (14.1, 14.2)*]. Trial T0821 was a phase 2 dose-finding placebo-controlled trial where otherwise healthy adult subjects 20 to 64 years of age received single oral dose of XOFLUZA or placebo. Trial T0831 was a placebo- and active-controlled trial in otherwise healthy adults and adolescents 12 to 64 years of age; subjects received weight-based XOFLUZA or placebo as a single oral dose on Day 1 or oseltamivir twice a day for 5 days. Trial T0832 was a randomized, double-blind, placebo- and active-controlled trial where adults and adolescents at high risk of influenza complications 12 years of age and older received either XOFLUZA, placebo or oseltamivir.

Table 2 displays the most common adverse events (regardless of causality assessment) reported in at least 1% of XOFLUZA adult and adolescent subjects who received XOFLUZA at the recommended dose in Trials T0821, T0831, and T0832.

Table 2 Incidence of Adverse Events Occurring in at Least 1% of Adult and Adolescent Subjects Receiving XOFLUZA in the Acute Uncomplicated Influenza Trials T0821, T0831, and T0832

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 (14.3)*].

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<http://sideeffects.health.gov.il>

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XOFLUZA

Baloxavir may form a chelate with polyvalent cations such as calcium, aluminum, or magnesium. Coadministration with polyvalent cation-containing products may decrease plasma concentrations of baloxavir [see *Clinical Pharmacology (12.3)*], which may reduce XOFLUZA efficacy.

Avoid 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).

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 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.

8.4 Pediatric Use

Treatment of Acute Uncomplicated Influenza in Adolescent Subjects (≥ 12 Years of Age)

The safety and effectiveness of XOFLUZA for the treatment of acute uncomplicated influenza in adolescent subjects 12 years of age and older weighing at least 40 kg is supported by one randomized, double-blind, controlled trial in otherwise healthy subjects Trial T0831 and one trial in subjects at high risk of developing influenza-related complications Trial T0832 [see *Clinical Studies (14.1)*]. A total of 117 otherwise healthy adolescents 12 to 17 years of age were randomized and received either XOFLUZA (N=76) or placebo (N=41) in Trial T0831; 38 adolescents 12 to 17 years of age at high risk for influenza complications were randomized and received either XOFLUZA (N=21) or placebo (N=17) in Trial T0832. The median time to alleviation of symptoms in influenza-infected adolescent subjects aged 12 to 17 years in Trial T0831 was comparable to that observed in adults. In Trial T0832, the median time to improvement of symptoms in the limited number of influenza-infected adolescent subjects aged 12 to 17 years was similar in the XOFLUZA and placebo arms [see *Clinical Studies (14.1)*]. Adverse events reported in adolescents in both trials were similar to those reported in adults [see *Adverse Reactions (6.1)*].

The safety and efficacy of XOFLUZA in pediatric subjects less than 12 years of age have not been established for the treatment of acute uncomplicated influenza. For information on baloxavir resistance in subjects less than 12 years of age [see *Microbiology (12.4)*].

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 T0834) [see *Clinical Studies (14.3)*]. 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 (14.3)*]. Adverse events reported in adolescent subjects were 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.

8.5 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 (14.2)*]. In Trial T0832, 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.

10 OVERDOSAGE

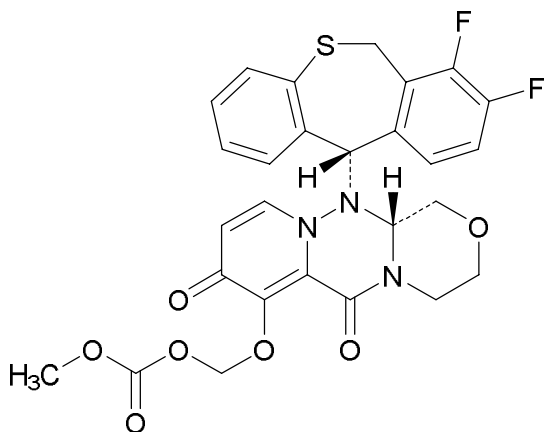
Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA.

Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

XOFLUZA (baloxavir marboxil) is an influenza virus 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]thiepin-11-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)methyl methyl carbonate. The empirical formula of baloxavir marboxil is C₂₇H₂₃F₂N₃O₇S, 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.

XOFLUZA tablets are white to light yellow, film-coated tablets for oral administration.

The 40 mg film-coated tablet contains 40 mg of baloxavir marboxil.

The inactive ingredients of XOFLUZA are: lactose monohydrate, croscarmellose sodium, povidone (K value:25), microcrystalline cellulose, sodium stearyl fumarate, talc, opadry white 03A48081 (hypromellose, talc and titanium dioxide(E171,C.I.77891)).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Baloxavir marboxil is an antiviral drug with activity against influenza virus [see *Microbiology (12.4)*].

12.2 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; 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.

12.3 Pharmacokinetics

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

Baloxavir pharmacokinetic parameters are presented for healthy adults and adolescents as the mean [% coefficient of variation (% CV)], unless otherwise specified, in Table 3. Absorption, distribution, metabolism, and elimination data for XOFLUZA is presented in Table 4.

Table 3 Pharmacokinetic Parameters of Plasma Baloxavir in Adults and Adolescents (≥ 12 Years of Age)

Pharmacokinetic Parameters of Plasma Baloxavir in Adults and Adolescents ^a	XOFLUZA dose 40 mg	XOFLUZA dose 80 mg
AUC (ng·hr/mL)	5520 (46.3%)	6930 (48.6%)
C _{max} (ng/mL)	68.9 (44.9%)	82.5 (43.0%)
C ₂₄ (ng/mL)	50.9 (45.8%)	62.6 (45.9%)
C ₇₂ (ng/mL)	24.2 (45.5%)	30.8 (47.0%)

^aTrial T0831 summary data, mean (%CV)

Table 4 Baloxavir Absorption, Distribution, Metabolism, Elimination Data

Absorption	
T _{max} (hr) ^a	4
Effect of food (relative to fasting) ^b	C _{max} : ↓ 48%, AUC _{0-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	
Clearance (CL/F, L/hr)	10.3 (22.5%)
Apparent terminal elimination half-life (hr)	79.1 (22.4%)
Metabolism	
Metabolic pathways	Primary: UGT1A3 Secondary: CYP3A4
Excretion	
% of dose excreted ^e	Urine: 14.7 (total radioactivity); 3.3 (baloxavir) Feces: 80.1 (total radioactivity)

^aMedian

^bMeal: approximately 400 to 500 kcal including 150 kcal from fat

^c*in vitro*

^dGeometric mean (geometric CV%)

^eRatio of radioactivity to radio-labeled baloxavir marboxil dose in mass balance study

No clinically significant differences in the pharmacokinetics of baloxavir were observed based on age, sex, creatinine clearance (CrCl: 50 mL/min and above) or moderate hepatic impairment (Child-Pugh class B). The effect of severe renal or hepatic impairment on baloxavir pharmacokinetics has not been evaluated.

Body Weight

Baloxavir exposure decreases as body weight increases.

No clinically significant difference in exposure was observed between body weight groups following the approved recommended dosage.

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 coadministered 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.

Animal Studies

Polyvalent Cations: In monkeys, a 48% to 63% decrease in baloxavir exposure was observed when XOFLUZA was coadministered with calcium, aluminum, magnesium, or iron. No study has been conducted in humans.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Both baloxavir marboxil and baloxavir do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 and do not induce CYP1A2, CYP2B6, or CYP3A4.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes: Both baloxavir marboxil and baloxavir do 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 does 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.

12.4 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 (IC₅₀) 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 (EC₅₀) 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 (EC₉₀) 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), E198K (A/H1N1) and E199G (A/H3N2) in the PA protein of the viral RNA polymerase complex.

Clinical Studies

Treatment-emergent substitutions were identified in influenza A and B viruses in clinical studies. Substitutions associated with a >3-fold reduction in susceptibility to baloxavir are shown in Table 5.

Table 5 Amino Acid Substitutions in PA Associated with Reduced Susceptibility to Baloxavir Identified in Clinical Specimens

Influenza Type/Subtype	A/H1N1	A/H3N2	B
Amino Acid Substitution	E23G/K/R, A37T, I38F/N/S/T	E23G/K, A37T, I38M/T, E199G	T20K, I38T

Clinical studies in adult and adolescent subjects ≥ 12 years of age:

In adult and adolescent subjects who had a confirmed influenza virus infection, the overall frequencies of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir were 5% (6/134), 11% (53/485), and 1% (2/224) in influenza A/H1N1, A/H3N2, and B virus infections, respectively, in pooled data from Trials T0821, T0831, and T0832 [see *Clinical Studies (14)*]. In Trial T0834, of 303 subjects ≥ 12 years of age who received XOFLUZA post-exposure prophylaxis, 32 were viral RNA-positive post-baseline, including 17 subjects who were evaluated for resistance. Of these 17 subjects, influenza virus with substitutions associated with reduced susceptibility to baloxavir was identified in 4/4 subjects who developed clinical influenza (as described for the primary endpoint) and 6/13 other subjects evaluated who did not meet the primary endpoint definition for clinical influenza [see *Clinical Studies (14)*].

Surveillance Studies

Amino acid substitutions associated with reduced susceptibility to baloxavir have also been identified in surveillance studies or in cell culture studies evaluating the impact of resistance substitutions identified in one influenza virus type/subtype on baloxavir susceptibility when introduced into other influenza virus types/subtypes (Table 6).

Table 6 Treatment-Emergent Amino Acid Substitutions in PA Associated with Reduced Susceptibility to Baloxavir Identified in Surveillance and in Cell Culture Resistance Studies

Influenza Type/Subtype	A/H1N1	A/H3N2	B
Amino Acid Substitution	A36V [†] , I38L [†] /M [‡]	E23R [‡] , A36V [‡] , I38F [‡] /N [‡] /S [‡]	I38F [‡] /M [‡] /N [‡] /S [‡]

[†] Identified in human surveillance isolates, antiviral treatment unknown

[‡] Known substitution associated with reduced susceptibility to baloxavir identified in clinical specimens or surveillance isolates but evaluated in the indicated alternative type/subtype by reverse genetics

None of the treatment-emergent substitutions associated with reduced susceptibility to baloxavir were identified in virus from pretreatment respiratory specimens in the clinical studies.

Treatment-emergent resistance has been associated with influenza virus rebound and prolonged virus shedding; however, the impact of prolonged shedding on clinical outcomes and virus transmission potential is currently unknown.

The frequency of baloxavir resistance and the prevalence of such resistant virus may vary seasonally and geographically. Prescribers should consider available information from the U.S. CDC and/or a local health department on current 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.

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.

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 or R292K, A/H7N9 virus with the NA substitution R292K (A/H3N2 numbering), and type B virus with the NA substitutions R152K or D198E (A/H3N2 numbering). 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 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 T0821, 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 T0821 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 T0831 (NCT02954354), a phase 3, randomized, double-blind, active- and placebo-controlled trial, XOFLUZA was studied in 1,436 otherwise healthy 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 aged 20 to 64 years received weight-based XOFLUZA (subjects who weighed 40 to less than 80 kg received 40 mg and subjects who weighed 80 kg and above received 80 mg) (N=612) or placebo as a single oral dose on day 1 (N=310) or oseltamivir twice a day for 5 days (N=514). 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 T0831 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 T0831, 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 T0821 and T0831, 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 T0821) or positive influenza reverse transcription polymerase chain reaction (RT-PCR) (Trial T0831) 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 7 and 8).

Table 7 Time to Alleviation of Symptoms After Single Dose in Otherwise Healthy Adults with Acute Uncomplicated Influenza in Trial T0821 (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)

^aCI: Confidence interval

^bXOFLUZA 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 8 Time to Alleviation of Symptoms After Single Dose in Otherwise Healthy Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial T0831 (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)

^aCI: Confidence interval

^bXOFLUZA 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 T0831, there was no difference in the time to alleviation of symptoms between subjects (age ≥ 20 years) who received XOFLUZA (54 hours) and those who received oseltamivir (54 hours). For adolescent subjects (12 to 17 years of age) in Trial T0831, 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 T0821 and 38 subjects in Trial T0831.

In the influenza B subset in Trial T0821, 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 T0831, 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.

14.2 Treatment of Acute Uncomplicated Influenza—High Risk Subjects (12 Years of Age and Older)

Trial T0832 (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 and Prevention definition¹ 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 T0832, 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 preexisting 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 preexisting 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 9).

Table 9 Time to Improvement of Symptoms After Single Dose in High Risk Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial T0832 (Median Hours)

XOFLUZA 40 mg or 80 mg^a (95% CI^b) N=385	Placebo (95% CI^b) N=385
73 hours ^c (67, 85)	102 hours ^c (93, 113)

^aThe dosage of XOFLUZA was based on subject’s weight.

^bCI: Confidence interval

^cXOFLUZA 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).

14.3 Post-Exposure Prophylaxis of Influenza

Trial T0834 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 a single dose of XOFLUZA according to body weight. The primary efficacy endpoint was the proportion of household subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom 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 T0834 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.

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 10).

Table 10 Proportion of Household Contacts (Subjects 12 Years of Age and Older) Infected with Influenza Virus with Fever and at Least One Respiratory Symptom (Trial T0834)

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

^aCI: 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

- 40 mg white to light yellow, oblong shaped film-coated tablets debossed with “BXM40” on one side available as:
 - 1 x 40 mg Film-coated tablets
 - 2 x 40 mg Film-coated tablets

Storage

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

Not all pack sizes might be marketed

Shelf-life

The expiry date of the product is indicated on the packaging materials.

17 MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

18 MARKETING AUTHORISATION NUMBER(S):

163-38-35956-00

19 manufacturer

F.Hoffmann-La Roche Ltd, Basel, Switzerland

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