

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

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.

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 (12.4) and Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

Initiate treatment with Xofluza within 48 hours of influenza symptom onset. Xofluza is taken orally as a single dose and may be taken with or without food. However, co-administration 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)*].

Adults and Adolescents (12 years of age and older)

The recommended dose of Xofluza in patients 12 years of age or older with acute uncomplicated Influenza is a single weight-based dose as follows:

Table 1 Recommended Xofluza Dosage in Adults and Adolescents 12 Years 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 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 post-marketing 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.

Treatment of Acute Uncomplicated Influenza

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

The safety profile of Xofluza is based on data from 2 placebo-controlled trials in which a total of 910 subjects received Xofluza: 834 (92%) were adults (18 years and older) and 76 (8%) were adolescents (12 to less than 18 years).

Of these, 710 subjects received Xofluza at the recommended dose.

In Trial 1, adult subjects 20 to 64 years of age received a single oral dose of Xofluza or placebo.

In Trial 2, adult subjects 20 to 64 years of age received Xofluza, placebo as a Xofluza single oral dose on Day 1, or oseltamivir twice a day for 5 days, and adolescent subjects 12 to less than 20 years of age received Xofluza or placebo as a single oral dose.

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 1 and 2.

Table 2 Incidence of Adverse Events Occurring in Greater Than or Equal to 1% of Subjects Receiving Xofluza in the Acute Uncomplicated Influenza Trials

Adverse Event	Xofluza (N = 710)	Placebo (N = 409)
Diarrhea	3%	5%
Bronchitis	2%	4%
Nausea	1%	1%
Nasopharyngitis	1%	1%
Headache	1%	2%

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 co-administration 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 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 (14)*]. The safety and effectiveness of Xofluza have not been established in pediatric patients less than 12 years of age.

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 [*see Clinical Studies (14)*]. 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. Adverse events reported in adolescents were similar to those reported in adults [*see Adverse Reactions (6.1)*].

8.5 Geriatric Use

Clinical trials of Xofluza did not include subjects 65 years of age and older to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

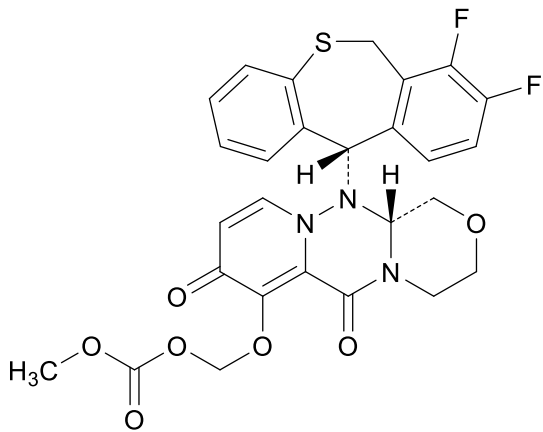
Treatment of an overdose of Xofluza should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Xofluza.

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

No change in the Xofluza baloxavir exposure-response (time to alleviation of symptoms) relationship was observed at the recommended dosing.

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 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 co-administered 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 Xofluz 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) and E199G (A/H3N2) in the PA protein of the viral RNA polymerase complex.

Clinical Studies

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

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 and 2 [see *Clinical Studies (14)*] were 2.7% (5/182) and 11% (39/370) respectively.

Table 5 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/S/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.

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 Xofluzo in otherwise healthy subjects with acute uncomplicated influenza.

In Trial T0821, a placebo-controlled phase 2 dose-finding trial, a single oral dose of Xofluzo 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 Xofluzo 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, Xofluzo 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 Xofluzo (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 Xofluzo and placebo arms received a placebo for the duration of oseltamivir dosing after Xofluzo or placebo dosing in that arm. Adolescent subjects 12 to less than 20 years of age received weight-based Xofluzo 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 (Xofluzo N=455, placebo N=230, or oseltamivir N=377). Among subjects who received Xofluzo 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 6 and 7).

Table 6 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 7 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.

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):

Xofluza 40 MG: 163-38-35956-00

19 MANUFACTURER

F.Hoffmann-La Roche Ltd, Basel, Switzerland

This leaflet was revised in January 2023 according to MOHs guidelines