

# Xofluza<sup>®</sup>



**Baloxavir Marboxil**

Film coated tablets

---

## **NAME OF THE MEDICINAL PRODUCT**

Xofluza 20 mg

Xofluza 40 mg

## **QUALITATIVE AND QUANTITATIVE COMPOSITION**

### Xofluza 20 mg film-coated tablets

Each tablet contains 20 mg baloxavir marboxil.

### Xofluza 40 mg film-coated tablets

Each tablet contains 40 mg baloxavir marboxil.

### Excipients with known effect

#### Lactose Intolerance

Each Xofluza 20mg tablet contains 77.9 mg lactose monohydrate.

Each Xofluza 40mg 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 20mg tablet contains 1.13 mg sodium

Each Xofluza 40mg 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), 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 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 *[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, 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 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 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 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<br>(N = 710) | Placebo<br>(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.

*Body as a Whole:* Swelling of the face, eyelids or tongue, dysphonia, angioedema, anaphylactic reactions, anaphylactic shock, anaphylactoid reactions

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

*Gastrointestinal disorders:* Vomiting, bloody diarrhea, melena, colitis

*Psychiatric:* Delirium, abnormal behavior, and 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**

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 available data on XOFLUZA use 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**

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.

### 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 [*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.

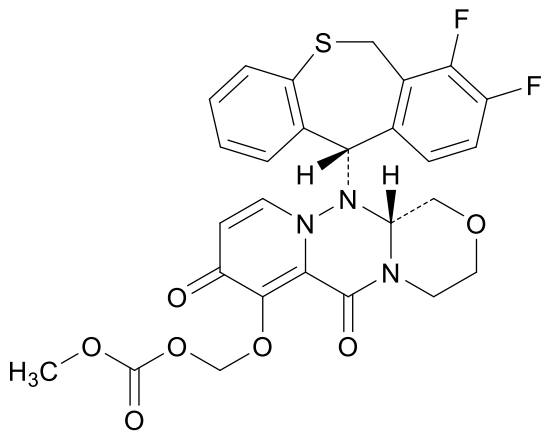
Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding [see *Clinical Pharmacology* (12.3)].

## 11 DESCRIPTION

XOFLUZA (baloxavir marboxil) is an antiviral PA endonuclease inhibitor. XOFLUZA is supplied as white to light yellow film-coated tablets for oral administration.

The active component of XOFLUZA is baloxavir marboxil. Baloxavir marboxil has a molecular weight of 571.55 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 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 C<sub>27</sub>H<sub>23</sub>F<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S and the chemical structure is shown below.



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.I77891)).

## 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 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.

In the phase 3 trial, at the recommended dose of 40 mg for subjects weighing less than 80 kg, the mean (CV%) values of baloxavir  $C_{max}$  and  $AUC_{0-inf}$  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  $AUC_{0-inf}$  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.

**Table 3 Pharmacokinetic Parameters of Plasma Baloxavir**

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

<sup>a</sup>Median

<sup>b</sup>Meal: approximately 400 to 500 kcal including 150 kcal from fat

<sup>c</sup>*in vitro*

<sup>d</sup>Geometric mean (geometric CV%)

<sup>e</sup>Apparent terminal elimination half-life

<sup>f</sup>Baloxavir is primarily metabolized by UGT1A3 with minor contribution from CYP3A4

<sup>g</sup>Ratio of radioactivity to radio-labeled [<sup>14</sup>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 co-administered 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.

## **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 (IC<sub>50</sub>) 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<sub>50</sub>) 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<sub>90</sub>) 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 and 2 [see *Clinical Studies (14)*] were 2.7% (5/182) and 11% (39/370) respectively.

**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.

## **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**

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 40 mg 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, 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)**

|                                       | <b>XOFLUZA 40 mg<br/>(95% CI<sup>a</sup>)<br/>N = 100</b> | <b>Placebo<br/>(95% CI<sup>a</sup>)<br/>N = 100</b> |
|---------------------------------------|---|---|
| <b>Adults (20 to 64 Years of Age)</b> | 50 hours <sup>b</sup><br>(45, 64)                         | 78 hours<br>(68, 89)                                |

<sup>a</sup>CI: Confidence interval

<sup>b</sup>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)**

|                                     | <b>XOFLUZA 40 mg or 80 mg<br/>(95% CI<sup>a</sup>)<br/>N = 455</b> | <b>Placebo<br/>(95% CI<sup>a</sup>)<br/>N = 230</b> |
|-------------------------------------|--|---|
| <b>Subjects (≥ 12 Years of Age)</b> | 54 hours <sup>b</sup><br>(50, 59)                                  | 80 hours<br>(73, 87)                                |

<sup>a</sup>CI: Confidence interval

<sup>b</sup>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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

XOFLUZA Tablets:

- 20 mg white to light yellow, oblong shaped film-coated tablets debossed with “Ⓢ772” on one side and “20” on the other side available as:
  - 2 x 20 mg Film-coated tablets
  - 4 x 20 mg Film-coated tablets
- 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

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 20 MG: 163-37-35948-00

XOFLUZA 40 MG: 163-38-35956-00

### **19     MANUFACTURER**

F.Hoffmann-La Roche ltd, Basel, Switzerland

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in **January 2020**