

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Xofluza 20 mg film-coated tablets

Xofluza 40 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

### Xofluza 20 mg

Each tablet contains 20 mg baloxavir marboxil.

### Excipient(s) with known effect

Each tablet contains 77.9 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

### Xofluza 40 mg

Each tablet contains 40 mg baloxavir marboxil.

### Excipient(s) with known effect

Each tablet contains 155.8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

### Xofluza 20 mg

White to light yellow, oblong shaped film-coated tablets approximately 8.6 mm in length, debossed with “⊗ 772” on one side and “20” on the other side.

### Xofluza 40 mg

White to light yellow, oblong shaped film-coated tablets approximately 11.1 mm in length, debossed on one side with “BXM40”.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

#### Treatment of influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and above.

#### Post-exposure prophylaxis of influenza

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

Xofluza should be used in accordance with official recommendations.

## 4.2 Posology and method of administration

### Posology

#### *Treatment of influenza*

A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours of symptom onset.

#### *Post-exposure prophylaxis of influenza*

A single dose of baloxavir marboxil should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza (see section 5.1).

#### *Adults and adolescents ( $\geq 12$ years of age)*

The recommended oral dose of baloxavir marboxil depending on body weight is shown in Table 1.

**Table 1. Baloxavir marboxil dosing by patient weight**

Patient body weight	Recommended oral dose
< 80 kg	Single dose of 40 mg taken as 2 x 20 mg tablets
$\geq 80$ kg	Single dose of 80 mg taken as 2 x 40 mg tablets

There are no clinical data on the use of a repeat dose of baloxavir marboxil for the treatment of uncomplicated influenza or for post-exposure prophylaxis in any one influenza season.

### Special populations

#### *Elderly ( $\geq 65$ years)*

No dosage adjustment is required (see section 5.2).

#### *Renal impairment*

No dose adjustment is required in patients with renal impairment (see section 5.2).

#### *Hepatic impairment*

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh class A or B). The safety and efficacy of baloxavir marboxil has not been established in patients with severe hepatic impairment (Child-Pugh class C).

#### *Paediatric population*

The safety and efficacy of baloxavir marboxil in children aged < 12 years has not been established.

### Method of administration

Oral use. The tablets should be taken with water.

Xofluza may be taken with or without food (see section 5.2).

Xofluza should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium (see section 4.5).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Lactose intolerance

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

#### Sodium

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

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Effects of other medicinal products on baloxavir marboxil or its active metabolite baloxavir

Products that contain polyvalent cations may decrease plasma concentrations of baloxavir. Xofluza should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium.

#### Immune response to influenza virus

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no or limited data from the use of baloxavir marboxil in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Xofluza during pregnancy.

#### Breast-feeding

It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk. Baloxavir marboxil and its metabolites are secreted in the milk of lactating rats.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to abstain from baloxavir marboxil therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## Fertility

No effects on male or female fertility were observed in animal studies performed with baloxavir marboxil (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xofluza has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

Hypersensitivity reactions have been observed in the postmarketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including urticaria and angioedema. Of these adverse reactions only urticaria has been observed in clinical studies with an estimated frequency category of “uncommon”.

### Tabulated list of adverse reactions

The following adverse drug reactions have been identified from postmarketing experience with baloxavir marboxil (Table 2) based on spontaneous case reports and cases from non-interventional study programmes. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**Table 2. Adverse drug reactions from postmarketing experience**

System Organ Class (SOC)	Adverse Reaction (preferred term, MedDRA)	Frequency
Immune system disorders	Anaphylaxis	Not known
	Anaphylactic reactions	Not known
	Hypersensitivity	Not known
Skin and subcutaneous disorders	Urticaria	Uncommon
	Angioedema	Not known

### Paediatric population

The safety profile in 109 adolescent patients ( $\geq 12$  years to  $< 18$  years) was similar to that in adult patients.

### 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Reports of overdoses with baloxavir marboxil have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse reactions were reported. Data are insufficient to determine what symptoms may be anticipated as a result of an overdose.

## Management

No known specific antidote exists for Xofluza. In the event of overdose, standard supportive medical care should be initiated based on the patient's signs and symptoms.

Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antivirals for systemic use, other anti-virals. ATC code: J05AX25.

#### Mechanism of action

Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza activity. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex and thereby inhibits the transcription of influenza virus genomes resulting in inhibition of influenza virus replication.

#### *In vitro activity*

The 50% inhibition concentration (IC<sub>50</sub>) of baloxavir was 1.4 to 3.1 nmol/L for influenza A viruses and 4.5 to 8.9 nmol/L for influenza B viruses in an enzyme inhibition assay.

In a MDCK cell culture assay, the median 50% effective concentration (EC<sub>50</sub>) values of baloxavir were 0.73 nmol/L (n=31; range: 0.20-1.85 nmol/L) for subtype A/H1N1 strains, 0.83 nmol/L (n=33; range: 0.35-2.63 nmol/L) for subtype A/H3N2 strains, and 5.97 nmol/L (n=30; range: 2.67-14.23 nmol/L) for type B strains.

In an MDCK cell-based virus titre reduction assay, the 90% effective concentration (EC<sub>90</sub>) values of baloxavir were in the range of 0.46 to 0.98 nmol/L for subtype A/H1N1 and A/H3N2 viruses, 0.80 to 3.16 nmol/L for avian subtype A/H5N1 and A/H7N9 viruses, and 2.21 to 6.48 nmol/L for type B viruses.

#### *Resistance*

Viruses bearing the PA/I38T/F/M/N mutation selected *in vitro* or in clinical studies show reduced susceptibility to baloxavir with changes in EC<sub>50</sub> values ranging from 11 to 57-fold for influenza A viruses and 2 to 8-fold for influenza B viruses.

In the two Phase 3 studies of treatment of uncomplicated influenza (see below) no resistance to baloxavir was detected in baseline isolates. Treatment-emergent mutations PA/I38T/M/N were detected in 36/370 (9.7%) and in 15/290 (5.2%) patients treated with baloxavir marboxil but were not detected in any patients treated with placebo.

In the Phase 3 study of post-exposure prophylaxis (see below), treatment-emergent mutations PA/I38T/M were found in 10 of 374 (2.7%) baloxavir marboxil-treated subjects. PA/I38 substitutions were not detected in placebo-treated subjects, with the exception of 2 subjects who received baloxavir marboxil as rescue medication.

Baloxavir is active *in vitro* against influenza viruses that are considered resistant to neuraminidase inhibitors, including strains with the following mutations: H274Y in A/H1N1, E119V and R292K in A/H3N2, R152K and D198E in type B virus, H274Y in A/H5N1, R292K in A/H7N9.

## Clinical trials

### *Treatment of uncomplicated influenza*

Capstone 1 (1601T0831), was a Phase 3 randomised, double-blind, multicentre study conducted in Japan and the US to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil compared with placebo and with oseltamivir in healthy adult and adolescent patients (aged  $\geq 12$  years to  $\leq 64$  years) with uncomplicated influenza. Patients were randomised to receive baloxavir marboxil (patients who weighed 40 to  $< 80$  kg received 40 mg and patients who weighed  $\geq 80$  kg received 80 mg), oseltamivir 75 mg twice daily for 5 days (only if aged  $\geq 20$  years) or placebo. Dosing occurred within 48 hours of first onset of symptoms.

A total of 1436 patients (of which 118 were aged  $\geq 12$  years to  $\leq 17$  years) were enrolled in the 2016-2017 Northern Hemisphere influenza season. The predominant influenza virus strain in this study was the A/H3 subtype (84.8% to 88.1%) followed by the B type (8.3% to 9.0%) and the A/H1N1pdm subtype (0.5% to 3.0%). The primary efficacy endpoint was time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) (TTAS). Baloxavir marboxil elicited a statistically significant reduction in TTAS when compared with placebo (Table 3).

**Table 3. Capstone 1: Time to alleviation of symptoms (baloxavir marboxil vs placebo)**

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

CI: Confidence interval

When the baloxavir marboxil group was compared to the oseltamivir group, there was no statistically significant difference in TTAS (53.5 h vs 53.8 h respectively).

The median (95% CI) TTAS was 49.3 (44.0, 53.1) and 82.1 (69.5, 92.9) hours for patients who were symptomatic for  $> 0$  to  $\leq 24$  hours, and 66.2 (54.4, 74.7) and 79.4 (69.0, 91.1) hours for patients who were symptomatic for  $> 24$  to  $\leq 48$  hours for baloxavir marboxil and placebo, respectively.

The median time to resolution of fever in patients treated with baloxavir marboxil was 24.5 hours (95% CI: 22.6, 26.6) compared with 42.0 hours (95% CI: 37.4, 44.6) in those receiving placebo. No difference was noted in duration of fever in the baloxavir marboxil group compared with the oseltamivir group.

Capstone 2 (1602T0832) was a Phase 3 randomised, double-blind, multicentre study to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil compared with placebo and with oseltamivir in adult and adolescent patients (aged  $\geq 12$  years) with uncomplicated influenza who had at least one host factor predisposing to the development of complications. Patients were randomised to receive a single oral dose of baloxavir marboxil (according to weight as in Capstone 1), oseltamivir 75 mg twice daily for 5 days, or placebo. Dosing occurred within 48 hours of first onset of symptoms.

Of the total 2184 patients 59 were aged  $\geq 12$  to  $\leq 17$  years, 446 were aged  $\geq 65$  to  $\leq 74$  years, 142 were aged  $\geq 75$  to  $\leq 84$  years and 14 were aged  $\geq 85$  years. The predominant influenza viruses in this study were the A/H3 subtype (46.9% to 48.8%) and influenza B (38.3% to 43.5%). The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) (TTIS). Baloxavir marboxil elicited a statistically significant reduction in TTIS when compared with placebo (Table 4).

**Table 4. Capstone 2: Time to improvement of influenza symptoms (baloxavir marboxil vs placebo)**

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

When the baloxavir marboxil group was compared to the oseltamivir group, there was no statistically significant difference in TTIS (73.2 h vs 81.0 h respectively).

The median (95% CI) TTIS was 68.6 (62.4, 78.8) and 99.1 (79.1, 112.6) hours for patients who were symptomatic for > 0 to ≤ 24 hours and 79.4 (67.9, 96.3) and 106.7 (92.7, 125.4) hours for patients who were symptomatic for > 24 to ≤ 48 hours for baloxavir marboxil and placebo, respectively.

For patients infected with type A/H3 virus, the median TTIS was shorter in the baloxavir marboxil group compared with the placebo group but not compared with the oseltamivir group (see Table 5). In the subgroup of patients infected with type B virus, the median TTIS was shorter in the baloxavir marboxil group compared with both the placebo and oseltamivir group (see Table 5).

**Table 5. Time to improvement of symptoms by influenza virus subtype**

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

The median time to resolution of fever was 30.8 hours (95% CI: 28.2, 35.4) in the baloxavir marboxil group compared with 50.7 hours (95% CI: 44.6, 58.8) in the placebo group. No clear differences between the baloxavir marboxil group and the oseltamivir group were observed.

The overall incidence of influenza-related complications (death, hospitalisation, sinusitis, otitis media, bronchitis, and/or pneumonia) was 2.8% (11/388 patients) in the baloxavir marboxil group compared with 10.4% (40/386 patients) in the placebo group. The lower overall incidence of influenza-related complications in the baloxavir marboxil group compared with the placebo group was mainly driven by lower incidences of bronchitis (1.8% vs. 6.0%, respectively) and sinusitis (0.3% vs. 2.1%, respectively).

#### *Post-exposure prophylaxis of influenza*

Study 1719T0834 was a Phase 3, randomised, double-blind, multicentre study conducted in 749 subjects in Japan to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil



compared with placebo for post-exposure prophylaxis of influenza. Subjects were household contacts of influenza-infected index patients.

A total of 607 subjects 12 years of age and over received either baloxavir marboxil dosed according to weight, as in the treatment studies, or placebo. The majority (74%) was enrolled within 24 hours of symptom onset in the index patient group. The predominant influenza virus strains in the index patients were the A/H3 subtype (49.1%) and the A/H1N1pdm subtype (46.2%) followed by influenza B (0.9%).

The primary efficacy endpoint was the proportion of household subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

There was a statistically significant reduction in the proportion of subjects with laboratory-confirmed clinical influenza from 13.6% in the placebo group to 1.9% in the baloxavir marboxil group (see Table 6).

**Table 6. Proportion of subjects with influenza virus, fever, and at least one respiratory symptom (baloxavir vs placebo)**

Proportion of Subjects with Influenza Virus, Fever, and at least one Respiratory Symptom (%) mITT population			
Baloxavir marboxil (95% CI)	Placebo (95% CI)	Risk Ratio (95% CI for risk ratio)	P-value
N=374 1.9 (0.8, 3.8)	N=375 13.6 (10.3, 17.5)	0.14 (0.06, 0.30)	< 0.0001
Proportion of Subjects $\geq$ 12 years with Influenza Virus, Fever, and at least one Respiratory Symptom (%)			
N=303 1.3 (0.4, 3.3)	N=304 13.2 (9.6, 17.5)	0.10 (0.04, 0.28)	< 0.0001

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xofluza in one or more subsets of the paediatric population for the treatment of influenza and prevention of influenza (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

After oral administration, baloxavir marboxil is extensively converted to its active metabolite, baloxavir. The plasma concentration of baloxavir marboxil is very low or below the limit of quantitation (< 0.100 ng/mL).

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

### Food effect

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

### Distribution

In an in-vitro study, the binding of baloxavir to human serum proteins, primarily albumin, is 92.9% to 93.9%. The apparent volume of distribution of baloxavir during the terminal elimination phase ( $V_z/F$ ) following a single oral administration of baloxavir marboxil is approximately 1180 litres in Caucasian subjects and 647 litres in Japanese subjects.

### Biotransformation

Baloxavir is primarily metabolised by UGT1A3 to form a glucuronide with a minor contribution from CYP3A4 to form a sulfoxide.

### Drug-drug interaction studies

Based on *in vitro* and *in vivo* drug-drug interaction (DDI) studies, baloxavir marboxil and baloxavir are not expected to inhibit isozymes of the CYP or UGT families or cause relevant induction of CYP enzymes.

Based on *in vitro* transporter studies and *in vivo* DDI studies, no relevant pharmacokinetic interaction is anticipated between baloxavir marboxil or baloxavir and medicines which are substrates of the following transporters: OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

### Excretion

Following a single oral administration of 40 mg of [ $^{14}C$ ]-labeled baloxavir marboxil, the proportion of total radioactivity excreted in faeces was 80.1% of the administered dose, with the urine accounting for 14.7% (3.3% and 48.7% of the administered dose was excreted as baloxavir in urine and faeces respectively).

### Elimination

The apparent terminal elimination half-life ( $t_{1/2,z}$ ) of baloxavir after a single oral administration of baloxavir marboxil is 79.1 hours in Caucasian subjects.

### Linearity/non-linearity

Following single oral administration of baloxavir marboxil, baloxavir exhibits linear pharmacokinetics within the dose range of 6 mg to 80 mg.

### Special populations

#### *Body weight*

Body weight is a significant covariate for baloxavir pharmacokinetics based on the population pharmacokinetic analysis. Dosing recommendations for baloxavir marboxil are based on body weight (see section 4.2).

#### *Gender*

A population pharmacokinetic analysis did not identify a clinically meaningful effect of gender on the pharmacokinetics of baloxavir. No dose adjustment based on gender is required.

#### *Race*

Based on a population pharmacokinetic analysis, race is a covariate on oral clearance (CL/F) of baloxavir in addition to body weight; however, no dose adjustment of baloxavir marboxil based on race is required.

#### *Age*

A population pharmacokinetic analysis using plasma baloxavir concentrations from clinical studies in subjects aged 12 to 64 years did not identify age as a relevant covariate on the pharmacokinetics of baloxavir.

#### *Paediatric population*

There are limited data on the pharmacokinetics of baloxavir in paediatric patients (< 12 years of age).

#### *Elderly*

Pharmacokinetic data collected in 181 patients aged  $\geq 65$  years show that exposure to baloxavir in the plasma was similar to that in patients aged  $\geq 12$  to 64 years.

#### *Renal impairment*

The effects of renal impairment on the pharmacokinetics of baloxavir marboxil or baloxavir have not been evaluated. Renal impairment is not expected to alter the elimination of baloxavir marboxil or baloxavir.

#### *Hepatic impairment*

No clinically meaningful differences in the pharmacokinetics of baloxavir were observed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B) compared with healthy controls with normal hepatic function.

The pharmacokinetics in patients with severe hepatic impairment have not been evaluated (see section 4.2).

### **5.3 Preclinical safety data**

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

Prolongation of PT and APTT were observed in rats at exposures at least equal to the human exposure based on  $AUC_{0-24hr}$  under specific experimental conditions, i.e. when fasted and when the food was either autoclaved or radiation-treated, resulting in vitamin K limiting/deficient conditions. These effects were not observed in monkey studies up to 4 weeks duration at the highest tested dose equivalent to 8-times the human exposure based on  $AUC_{0-24hr}$ . They are considered to be of limited clinical relevance.

Carcinogenicity studies have not been performed with baloxavir marboxil.

The pro-drug baloxavir marboxil, and its active form, baloxavir, were not considered genotoxic as they tested negative in bacterial reverse mutation tests, micronucleus tests with cultured mammalian cells, and as baloxavir marboxil was negative in an *in vivo* rodent micronucleus test.

Baloxavir marboxil had no effects on fertility when given orally to male and female rats at doses providing exposure equivalent to 5-times the human exposure based on  $AUC_{0-24hr}$ .

Baloxavir marboxil did not cause malformations in rats or rabbits.

The oral embryo-foetal development study of baloxavir marboxil in rats with daily doses from gestation day 6 to 17 revealed no signs of maternal or foetal toxicity up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on  $AUC_{0-24hr}$ .

In rabbits, a dose providing exposure equivalent to 14-times the human exposure based on AUC<sub>0-24hr</sub> following the MHRD caused maternal toxicity resulting in miscarriages and significant increase in incidence of foetuses with a skeletal variation (cervical rib). The skeletal variations were reabsorbed during the growing process of adjacent cervical vertebra. A dose providing exposure equivalent to 6-times the human exposure based on AUC<sub>0-24hr</sub> in rabbits was without adverse effects.

The pre- and postnatal study in rats did not show drug-related adverse findings in dams and pups up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on AUC<sub>0-24hr</sub>.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Lactose monohydrate  
Croscarmellose sodium (E468)  
Povidone (K25)  
Microcrystalline cellulose (E460)  
Sodium stearyl fumarate

#### Film-coating

Hypromellose  
Talc (E553b)  
Titanium dioxide (E171)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special temperature storage conditions.  
Store in the original package in order to protect from moisture.

### **6.5 Nature and contents of container**

Blister pack (OPA/Aluminum foil/PVC, sealed with aluminium foil).

Pack of 2 tablets.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1500/001  
EU/1/20/1500/002

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG  
Emil-Barell-Strasse 1  
D-79639 Grenzach-Wyhlen  
Germany

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit a PSUR for this product within 6 months following authorisation.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**



## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xofluza 20 mg film-coated tablets  
baloxavir marboxil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 20 mg baloxavir marboxil.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

2 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use  
Oral use  
Take both tablets as a single dose

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from moisture

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1500/001

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xofluza 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTERS</b>
-----------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xofluza 20 mg film-coated tablets  
baloxavir marboxil

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Roche Registration GmbH

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xofluza 40 mg film-coated tablets  
baloxavir marboxil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 40 mg baloxavir marboxil.

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

2 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use  
Oral use  
Take both tablets as a single dose

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from moisture

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
Germany

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/20/1500/002

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

Xofluza 40 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTERS</b>
-----------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xofluza 40 mg film-coated tablets  
baloxavir marboxil

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Roche Registration GmbH

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

## **B. PACKAGE LEAFLET**



## **Package leaflet: Information for the patient**

**Xofluza 20 mg film-coated tablets**

**Xofluza 40 mg film-coated tablets**

baloxavir marboxil

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Xofluza is and what it is used for
2. What you need to know before you take Xofluza
3. How to take Xofluza
4. Possible side effects
5. How to store Xofluza
6. Contents of the pack and other information

### **1. What Xofluza is and what it is used for**

#### **What Xofluza is**

Xofluza contains baloxavir marboxil. This is a type of antiviral medicine called a ‘cap-dependent endonuclease inhibitor’.

Xofluza is used for treating and preventing influenza. This medicine stops the influenza virus from spreading in the body and helps shorten the time to recovery from symptoms.

#### **What Xofluza is used for**

- Xofluza is used to treat influenza in patients aged 12 years and above who have had influenza symptoms for less than 48 hours.
- Xofluza is used to prevent influenza in individuals aged 12 years and above who have been in close contact with someone who is known or suspected to have influenza.

### **2. What you need to know before you take Xofluza**

#### **Do not take Xofluza if:**

- you are allergic to baloxavir marboxil or any of the other ingredients of this medicine (listed in section 6).

#### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Xofluza.

## **Children and adolescents**

Do not give this medicine to children below 12 years of age. This is because the effects of Xofluza in this age group are not known.

## **Other medicines and Xofluza**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Xofluza with:

- laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium, or magnesium

The medicines listed above may decrease the effect of Xofluza.

## **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, as a precautionary measure it is preferable to avoid the use of Xofluza. Ask your doctor or pharmacist for advice before taking this medicine.

## **Driving and using machines**

Xofluza is not likely to change your ability to drive and to use machines.

## **Xofluza contains lactose**

Xofluza contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

## **Xofluza contains sodium**

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

## **3. How to take Xofluza**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

### **How to take Xofluza**

For treatment of influenza, take Xofluza as a single dose as soon as possible within 48 hours of your flu symptoms starting.

For prevention of influenza, take Xofluza as a single dose as soon as possible within 48 hours following exposure to an infected person.

### **How much Xofluza to take**

Your dose of Xofluza depends on how much you weigh. Your doctor or pharmacist will tell you how much to take.

Your weight	Xofluza dose
Up to 80 kg	Single dose of 40 mg taken as - 2 x 20 mg tablets
80 kg or more	Single dose of 80 mg taken as - 2 x 40 mg tablets

Xofluza can be taken with or without food. Take all the tablets with some water.

### **If you take more Xofluza than you should**

If you accidentally take more of this medicine than you should, talk to your doctor or pharmacist for advice.

### **If you forget to take Xofluza**

If you forget to take some or all of your dose, take it as soon as possible.

For the treatment of influenza, Xofluza should be taken within 48 hours of your flu symptoms starting.

For the prevention of influenza, Xofluza should be taken within 48 hours of close contact with someone who is known or suspected to have flu.

## **4. Possible side effects**

Like all medicines, it is possible for this medicine to cause side effects, although not everybody gets them.

### **Get medical help immediately if you get any of the following serious side effects:**

- Severe allergic reaction (anaphylaxis), with signs such as swelling of the face or skin, itchy rashes, low blood pressure and difficulty breathing

The frequency of these side effects cannot be estimated from the available data.

### **Other possible side effects:**

The following side effect is **uncommon** (this can affect up to 1 in every 100 patients):

- Itchy rash

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Xofluza**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not need any special temperature storage conditions.

Store in the original package in order to protect from moisture.


Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Xofluza contains**

- The active substance is baloxavir marboxil.
- Each 20 mg film-coated tablet contains 20 mg baloxavir marboxil. Each 40 mg film-coated tablet contains 40 mg baloxavir marboxil.
- The other ingredients are lactose monohydrate, croscarmellose sodium (E468), povidone, microcrystalline cellulose (E460), sodium stearyl fumarate in the tablet core, and hypromellose, talc (E553b) and titanium dioxide (E171) in the film-coating.

### **What Xofluza looks like and contents of the pack**

Xofluza 20 mg tablets are white to light yellow, oblong shaped film-coated tablets with “ 772” marked on one side and “20” on the other side.

Xofluza 20 mg film-coated tablets are available in blister packs of 2.

Xofluza 40 mg tablets are white to light yellow, oblong shaped film-coated tablets with “BXM40” marked on one side.

Xofluza 40 mg film-coated tablets are available in blister packs of 2.

### **Marketing Authorisation Holder**

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
Germany

### **Manufacturer**

Roche Pharma AG  
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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.