▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
Xofluza® (baloxavir marboxil) tablets

1. NAME OF THE MEDICINE

Baloxavir marboxil.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mg film-coated tablet contains 20 mg baloxavir marboxil.
Each 40 mg film-coated tablet contains 40 mg baloxavir marboxil.

Excipients with known effect

Each 20 mg tablet contains 77.9 mg of lactose monohydrate and each 40 mg tablet contains 155.8 mg of lactose monohydrate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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 on one side with "BXM40".

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

- otherwise healthy, or
- at high risk of developing influenza complications.

4.2 DOSE AND METHOD OF ADMINISTRATION

A single oral dose of Xofluza should be taken within 48 hours of symptom onset.

Xofluza may be taken with or without food (see section 5.2 Pharmacokinetic Properties). Avoid co-administration of Xofluza with calcium-fortified beverages, polyvalent cation-

containing laxatives, antacids or oral supplements, e.g., calcium, iron, magnesium, selenium, or zinc. Where possible, avoid co-administration of Xofluza with dairy products (see section 4.5).

Dose

Adults and Adolescents (≥ 12 years of age)

The recommended dose of Xofluza depending on body weight is shown in Table 1.

Table 1 Xofluza dosing by patient weight

Patient Body Weight	Recommended Oral Dose
40 kg to < 80 kg	40 mg
≥ 80 kg	80 mg

Dosage modifications

No dose reductions of Xofluza are recommended.

Special populations

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment (see section 5.2 Pharmacokinetics in special populations, Hepatic impairment). Xofluza has not been studied in patients with severe hepatic impairment.

Renal impairment

The safety and efficacy of Xofluza has not been studied in patients with renal impairment. A change in dose is not required for patients with renal impairment (see section 5.2 Pharmacokinetics in special populations, Renal impairment).

Elderly

No dosage adjustment is recommended in elderly patients (see section 5.2 Pharmacokinetics in special populations, Elderly).

Paediatric populations

The safety and efficacy of Xofluza in patients < 12 years of age has not been established. For patients ≥ 12 years weighing at least 40 kg, see Table 1.

4.3 CONTRAINDICATIONS

Xofluza is contraindicated in patients with a known hypersensitivity to baloxavir marboxil or to any of the excipients (see section 4.8 Post-marketing Experience).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR 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

medicines. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use Xofluza.

Hypersensitivity

Hypersensitivity reactions after use of Xofluza have been reported in post-marketing surveillance. While in several cases a definitive causal relationship could not be confirmed, cases of hypersensitivity (including anaphylaxis, facial/throat swelling, skin eruptions and urticaria) have been attributed to exposure to baloxavir. Appropriate treatment should be instituted if an allergic-like reaction occurs or is suspected.

Use in hepatic impairment

The safety and efficacy of Xofluza in patients with severe hepatic impairment has not been studied. Refer to sections 4.2 Dose, Special populations, Hepatic impairment and 5.2 Pharmacokinetics in special populations, Hepatic impairment.

Use in renal impairment

The safety and efficacy of Xofluza in patients with renal impairment has not been studied. Refer to sections 4.2 Dose, Special populations, Renal impairment and 5.2 Pharmacokinetics in special populations, Renal impairment.

Use in the elderly

The safety and efficacy of Xofluza for the treatment of influenza in geriatric patients age ≥ 65 years and weighing at least 40 kg have been established. Refer to sections 4.2 Dose, Special populations, Elderly and 5.2 Pharmacokinetics in special populations, Elderly.

Paediatric use

The safety and efficacy in paediatric patients (< 12 years of age and/or weighing < 40 kg) has not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically significant drug-drug interactions are anticipated between baloxavir marboxil or its active metabolite, baloxavir, and substrates, inhibitors, or inducers of cytochrome P450 (CYP enzymes), inhibitors of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) enzyme, or gut or renal transporters.

Polyvalent cation containing products may decrease plasma concentrations of baloxavir. Xofluza should not be taken with calcium-fortified beverages, polyvalent cation containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, magnesium. Where possible, avoid co-administration of Xofluza with dairy products.

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.

Effects of other medicines on baloxavir marboxil or its active metabolite baloxavir

Baloxavir marboxil and baloxavir are substrates for P-glycoprotein (P-gp). Itraconazole, an inhibitor of P-gp, increased the C_{max} and $AUC_{0\text{-}inf}$ of baloxavir 1.33-fold and 1.23-fold, respectively. These increases are not considered to be clinically meaningful.

Probenecid, an inhibitor of UGT enzyme, decreased the C_{max} and $AUC_{0\text{-}inf}$ of baloxavir by 21% and 25%, respectively. These decreases are not considered to be clinically meaningful.

Effects of baloxavir marboxil or its active metabolite baloxavir on other medicines

In *in vitro* studies at clinically relevant concentrations, baloxavir marboxil and its active metabolite, baloxavir, did not inhibit any of the following isozymes of the CYP or UGT family: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 isozymes. In in vitro studies at clinically relevant concentrations, baloxavir marboxil and baloxavir did not cause significant induction of CYP1A2, CYP2B6, and CYP3A4.

In *in vitro* transporter studies at clinically relevant concentrations, baloxavir marboxil inhibited the efflux transporter (P-gp). Baloxavir, but not baloxavir marboxil, inhibited Breast Cancer Resistance Protein (BCRP).

Baloxavir is not an inhibitor of BSEP or OAT1 *in vitro*. Based on *in vitro* transporter studies, despite a weak *in vitro* inhibitory potential, baloxavir is not expected to be an *in vivo* inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT3, MATE1, or MATE2K. Hence, no relevant pharmacokinetic interaction is anticipated between baloxavir and medicines which are substrates of these transporters.

A single 40 mg dose of baloxavir marboxil did not affect the pharmacokinetics of midazolam, a substrate of CYP3A4, suggesting that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of CYP3A.

A single 80 mg dose of baloxavir marboxil did not affect the pharmacokinetics of digoxin, a substrate of P-gp, suggesting that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of P-gp.

A single 80 mg dose of baloxavir marboxil decreased C_{max} and $AUC_{0\text{-}inf}$ of rosuvastatin, a substrate of BCRP, by 18% and 17%, respectively. These decreases are not considered to be clinically meaningful and indicate that baloxavir marboxil or baloxavir is not expected to affect the pharmacokinetics of co-administered drugs that are substrates of BCRP.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Baloxavir marboxil had no effects on fertility when given orally to male and female rats at doses up to 1000 mg/kg/day, which is equivalent to 2-times the human exposure based on $AUC_{0\text{-}24hr}$ at the maximum recommended human dose.

Use in pregnancy - Category B3

There are no adequate and well-controlled studies with Xofluza in pregnant women. The potential risk of Xofluza in pregnant women is unknown. Xofluza should be avoided during pregnancy unless the potential benefit justifies the potential risk to the fetus.

A tissue distribution study in pregnant rats showed that baloxavir crosses the placenta. Baloxavir marboxil did not cause malformations in rats or rabbits. The oral embryo-fetal development study of baloxavir marboxil in rats with daily doses from gestation day 6 to 17 revealed no signs of fetal toxicity up to the highest tested dose of 1000 mg/kg/day, which is equivalent to 2-times the human exposure based on $AUC_{0\text{-}24hr}$ at the maximum recommended human dose.

In rabbits, a dose level of 1000 mg/kg/day (equivalent to 6-times the human exposure based on $AUC_{0\text{-}24hr}$ following the maximum recommended human dose) caused maternal toxicity resulting in 2 miscarriages out of 19 and an increased incidence of fetuses with a skeletal variation (cervical rib), but no malformations. A dose of 100 mg/kg/day (equivalent to 3-times the human exposure based on $AUC_{0\text{-}24hr}$) 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 of 1000 mg/kg/day, which is equivalent to 2-times the human exposure based on $AUC_{0\text{-}24hr}$.

Labour and delivery

The safe use of Xofluza during labour and delivery has not been established.

Use in lactation

It is not known whether baloxavir marboxil and the active metabolite, baloxavir, are excreted in human breast milk. When dosed at 1 mg/kg, baloxavir marboxil or its metabolites are secreted in the milk of lactating rats.

A decision should be made whether to discontinue nursing or to initiate treatment with Xofluza, taking into consideration the potential benefit of Xofluza to the nursing mother and the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and to use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

The overall safety profile of Xofluza is based on data from 2109 subjects in 17 clinical trials receiving Xofluza. No adverse drug reactions have been identified based on pooled data from 3 placebo-controlled clinical studies (studies 1518T0821, CAPSTONE-1 and CAPSTONE-2) in adult and adolescent patients, in which a total of 1640 patients have received Xofluza. This includes otherwise healthy adults and adolescents and patients at high risk of developing complications associated with influenza, e.g. elderly patients and patients with chronic cardiac or respiratory disease. Of these, 1334 patients (81.3%) were adults from 18 years to 64 years or lower, 209 patients (12.7%) were adults at least 65 years of age or older, and 97 patients (5.9%) were adolescents at least 12 years to 18 years of age. Of these, 1440 patients received Xofluza at the recommended dose. The safety profile in patients at high risk was similar to that in otherwise healthy adults and adolescents.

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 studies 1518T0821, CAPSTONE-1 and CAPSTONE-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=1440)	Placebo (N=1136)
Diarrhoea	3%	4%
Bronchitis	3%	4%
Nausea	2%	3%
Sinusitis	2%	3%
Headache	1%	1%

Post-marketing experience

The following adverse effects have been identified during post-marketing use of Xofluza. Because these effects 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 disorder: Anaphylaxis, anaphylactic reactions, hypersensitivity.

Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash.

Gastrointestinal disorders: Vomiting, bloody diarrhoea, melaena, ischemic colitis.

Description of selected adverse drug reactions from post-marketing experience

Hypersensitivity reactions have been observed in the post-marketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including angioedema, urticaria and rash.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Clinical experience

Reports of overdose have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported. From the limited number of cases associated with adverse events, 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Baloxavir marboxil is a prodrug that is converted by hydrolysis to its active metabolite, 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. The 50% inhibition concentration (IC_{50}) 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.

Nonclinical studies demonstrate potent antiviral activity of baloxavir against influenza A and B virus *in vitro* and *in vivo*. The antiviral activity of baloxavir against laboratory strains and clinical isolates of influenza A and B viruses was determined in the MDCK cell culture assay. The median 50% effective concentration (EC_{50}) values of baloxavir were 0.73 nmol/L (n=31; range: 0.20 to 1.85 nmol/L) for subtype A/H1N1 strains, 0.83 nmol/L (n=33; range: 0.35 to 2.63 nmol/L) for subtype A/H3N2 strains, and 5.97 nmol/L (n=30; range: 2.67 to 14.23 nmol/L) for type B strains. In a MDCK cell-based virus titre reduction assay, the 90% effective concentration (EC_{90}) 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.

Viruses bearing the PA/I38T/M mutation selected *in vitro* or in clinical studies show reduced susceptibility to baloxavir. Baloxavir is active against neuraminidase inhibitor resistant strains including H274Y in A/H1N1, E119V and R292K in A/H3N2, and R152K and D198E in type B virus, H274Y in A/H5N1, R292K in A/H7N9.

The relationship between antiviral activity in cell culture and inhibition of influenza virus replication in humans has not been established.

Viral resistance

Resistance Monitoring during Clinical Development

Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir have been detected 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 observed in amino acid substitutions I38T (H1N1 and H3N2) and E199G (H3N2) in the polymerase acidic (PA) protein of the viral RNA polymerase complex. Influenza B virus isolates with reduced susceptibility to baloxavir have not been detected in cell culture.

Clinical studies: Influenza A virus isolates with treatment-emergent amino acid substitutions at position PA/I38T/F/M associated with > 10-fold reduced susceptibility to baloxavir were observed in clinical studies. The clinical impact of this reduced susceptibility is unclear.

No pre-treatment isolates, with amino acid substitutions associated with reduced susceptibility to baloxavir, were found in the clinical studies or in the National Center for Biotechnology Information/Influenza virus resources database.

In the phase 3 study in otherwise healthy patients (CAPSTONE-1), PA/I38T/M were detected in 36 of 370 patients (9.7%) in the Xofluza treatment group. In the phase 3 study in high risk patients (CAPSTONE-2), PA/I38T/M/N were detected in 15 of 290 patients (5.2%) in the Xofluza treatment group.

Prescribers should consider available information from the WHO and/or local government websites on influenza drug susceptibility patterns and treatment effects when deciding whether to use Xofluza.

Cross Resistance

No single amino acid substitution has been identified that could confer cross-resistance between baloxavir and neuraminidase inhibitors (e.g., peramivir, oseltamivir, zanamivir). However, a virus may carry amino acid substitutions associated with reduced susceptibility to baloxavir in the PA protein and to neuraminidase inhibitors in the neuraminidase and may therefore exhibit reduced susceptibility to both classes of inhibitors. The clinical relevance of phenotypic cross resistance evaluations has not been established.

Pharmacodynamic effects

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

Clinical trials

Clinical trials for the approved indication of treatment of patients with uncomplicated influenza are described in this section. Prophylaxis of influenza is outside the scope of the current indication.

Clinical trials in Otherwise Healthy patients

CAPSTONE-1 (Study 1601T0831)

CAPSTONE-1 is a randomised, double-blind, multicentre, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo or oseltamivir in otherwise healthy adult and adolescent patients (aged ≥ 12 years to ≤ 64 years) with influenza. Patients infected with human immunodeficiency virus (HIV) or with cancer were not enrolled in this study.

A total of 1436 patients were randomised to receive treatment in the 2016-2017 Northern Hemisphere influenza season. Patients were randomised to receive 40 mg or 80 mg of Xofluza according to weight (< 80 kg or ≥ 80 kg respectively), oseltamivir 75 mg twice daily for 5 days (if aged > 20 years) or placebo. The primary efficacy population was defined as those who received study medication and had a positive influenza reverse transcription polymerase chain reaction (RT-PCR) result at trial entry.

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). A statistically significant and clinically meaningful improvement in the primary endpoint was seen for Xofluza when compared with placebo (Table 3).

Table 3 Primary efficacy endpoint: Time to alleviation of symptoms in Otherwise Healthy patients with influenza (Xofluza vs Placebo)

Median Time to Alleviation of Symptoms (Hours)			
Xofluza 40/80 mg[1] (95% CI) N=455	Placebo (95% CI) N=230	Difference between Xofluza and placebo (95% CI for difference)	P-value[2]
53.7 (49.5, 58.5)	80.2 (72.6, 87.1)	-26.5 (−35.8, −17.8)	< 0.0001

CI = confidence interval

[1] Dosing was based on weight. Patients weighing < 80 kg received a single 40 mg dose and patients ≥ 80 kg received a single 80 mg dose

[2] P-values based on the stratified generalised Wilcoxon test. Stratification factors: composite symptom scores at baseline and region

Secondary efficacy endpoints

When the Xofluza group was compared to the oseltamivir group, there was no statistically significant difference in time to alleviation of symptoms (53.5 h vs 53.8 h respectively) (Table 4).

Table 4 Time to alleviation of symptoms in Otherwise Healthy patients (≥ 20 years of age) with influenza (Xofluza vs oseltamivir)

Median Time to Alleviation of Symptoms (hours)			
Xofluza 40/80 mg[1] (95% CI) N=375	Oseltamivir (95% CI) N=377	Difference between Xofluza and oseltamivir (95% CI for difference)	P-value[2]
53.5 (48.0, 58.5)	53.8 (50.2, 56.4)	-0.3 (−6.6, 6.6)	0.7560

CI = confidence interval

[1] Dosing was based on weight. Patients weighing < 80 kg received a single 40 mg dose and patients ≥ 80 kg received a single 80 mg dose

[2] P-values based on the stratified generalised Wilcoxon test. Stratification factors: composite symptom scores at baseline and region

Resolution of Fever: Following study drug administration there was faster resolution of fever in the Xofluza group compared with the placebo group. The median time to resolution of fever in patients treated with Xofluza 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 Xofluza group compared with the oseltamivir group.

Antiviral Activity: Patients treated with Xofluza showed a rapid reduction in virus titre. The median time to cessation of viral shedding determined by virus titre was 24.0 hours (95% CI: 24.0, 48.0) in the Xofluza group compared with 72.0 hours (95% CI: 72.0, 96.0) in the oseltamivir group and 96.0 hours (95% CI: 96.0, 96.0) in the placebo group.

Study 1518T0821

The phase 2 study was designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared with placebo in otherwise healthy adult patients (aged ≥ 20 years to ≤ 64 years) with influenza. A total of 400 patients were randomised to one of three dose groups of Xofluza (10 mg, 20 mg or 40 mg) or placebo in the 2015-2016 Northern Hemisphere influenza season in Japan. The predominant influenza virus strain was A/H1N1pdm subtype (61% to 71%) followed by B subtype (21% to 24%) and A/H3N2 subtype (5% to 13%).

The median time to alleviation of symptoms (primary efficacy endpoint) was significantly shorter ($p < 0.05$) compared with placebo in all dose groups. At 40 mg, the median time to alleviation of symptoms was 49.5 hours (95% CI: 44.5, 64.4) versus 77.7 hours (95% CI: 67.6, 88.7) in the placebo group.

Resolution of Fever (secondary efficacy endpoint): The median time to resolution of fever was significantly reduced in all dose groups compared with placebo. At 40 mg, the median time was 28.9 hours (95% CI: 24.5, 34.7) versus 45.3 hours (95% CI: 35.6, 54.0) in the placebo group. Viral endpoint results were consistent with those in CAPSTONE-1.

Clinical trials in High Risk patients

CAPSTONE-2 (Study 1602T0832)

CAPSTONE-2 is a randomised, double-blind, multicentre, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of Xofluza compared

with placebo or oseltamivir in adult and adolescent patients (aged ≥ 12 years) with influenza at high risk of influenza complications (e.g. asthma or chronic lung disease, endocrine disorders, heart disease, age ≥ 65 years, metabolic disorders, morbid obesity). Patients who had cancer within the last 5 years (other than non-melanoma skin cancer), untreated HIV infection, or treated HIV infection with a CD4 count below 350 cells/mm^3 in the last 6 months, were not enrolled in this study.

A total of 2184 patients were randomised to receive a single oral dose of 40 mg or 80 mg of Xofluza according to body weight (40 kg to < 80 kg or ≥ 80 kg respectively), oseltamivir 75 mg twice daily for 5 days, or placebo. The primary efficacy population was defined as those who received study medication, had a positive influenza RT-PCR at trial entry and were enrolled at sites with Good Clinical Practice (GCP) compliance.

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). A statistically significant improvement in the primary endpoint was observed for Xofluza when compared with placebo (Table 5).

Table 5 Primary efficacy endpoint: Time to improvement of influenza symptoms in High Risk patients (Xofluza vs Placebo)

Median Time to Improvement of Influenza Symptoms (hours)			
Xofluza 40/80 mg[1] (95% CI) N=385	Placebo (95% CI) N=385	Difference between Xofluza and placebo (95% CI for difference)	P-value[2]
73.2 (67.5, 85.1)	102.3 (92.7, 113.1)	-29.1 (−42.8, −14.6)	< 0.0001

CI = confidence interval

[1] Dosing was based on weight. Patients weighing < 80 kg received a single 40 mg dose and patients ≥ 80 kg received a single 80 mg dose

[2] P-values based on the stratified generalised Wilcoxon test. Stratification factors: region, composite symptom scores at baseline, and pre-existing and worsened symptoms

Secondary efficacy endpoints

When the Xofluza group was compared to the oseltamivir group, there was no statistically significant difference in time to improvement of influenza symptoms (73.2 h vs 81.0 h respectively) (Table 6).

Table 6 Time to improvement of influenza symptoms in High Risk patients (Xofluza vs oseltamivir)

Median Time to Improvement of Influenza Symptoms (hours)			
Xofluza 40/80 mg[1] (95% CI) N=385	Oseltamivir (95% CI) N=388	Difference between Xofluza and oseltamivir (95% CI for difference)	P-value[2]
73.2 (67.5, 85.1)	81.0 (69.4, 91.5)	-7.7 (−22.7, 7.9)	0.8347

CI = confidence interval

[1] Dosing was based on weight. Patients weighing < 80 kg received a single 40 mg dose and patients ≥ 80 kg received a single 80 mg dose

[2] P-values based on the stratified generalised Wilcoxon test. Stratification factors: region, composite symptom scores at baseline, and pre-existing and worsened symptom

For patients infected with type A/H3 virus (predominant strain), the median time to improvement of influenza symptoms was shorter in the Xofluza group compared with the placebo group but not when compared with the oseltamivir group (Table 7). In the subgroup of patients infected with type B virus, the median time to improvement of influenza symptoms was shorter in the Xofluza group compared with both the placebo and oseltamivir group.

Table 7 Time to improvement of symptoms by influenza virus subtype

Median Time to Improvement of Symptoms (Hours)			
Virus	Xofluza 40/80 mg[1] (95% CI)	Placebo (95% CI)	Oseltamivir (95% CI)
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

CI = confidence interval

[1] Dosing was based on weight. Patients weighing < 80 kg received a single 40 mg dose and patients ≥ 80 kg received a single 80 mg dose

Resolution of Fever: The proportion of patients who had fever was reduced more rapidly in the Xofluza group than in the placebo group following study drug administration. The median time to resolution of fever was 30.8 hours (95% CI: 28.2, 35.4) in the Xofluza group compared with 50.7 hours (95% CI: 44.6, 58.8) in the placebo group. No clear differences between the Xofluza group and the oseltamivir group were observed.

Incidence of Influenza-Related Complications: The overall incidence of influenza-related complications (death, hospitalisation, sinusitis, otitis media, bronchitis, and/or pneumonia) was 2.8% (11/388 patients) in the Xofluza group compared with 10.4% (40/386 patients) in the placebo group and 4.6% (18/389 patients) in the oseltamivir group. The lower overall incidence of influenza-related complications in the Xofluza 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).

The proportion of patients requiring systemic antibiotics for infections secondary to influenza infection was lower in the Xofluza group (3.4%) compared with the placebo group (7.5%) and the difference between these 2 groups was statistically significant (p=0.0112). The proportion of patients requiring systemic antibiotics in the Xofluza group was comparable with the proportion in the oseltamivir group (3.9%).

Antiviral Activity: Patients at high risk of influenza complications treated with Xofluza showed a rapid reduction in virus titre and a significantly shortened time to cessation of viral shedding. The median time to cessation of viral shedding determined by virus titre was 48 hours in the Xofluza group compared with 96 hours in the placebo and oseltamivir groups.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, baloxavir marboxil is extensively converted to its active metabolite (baloxavir) predominantly by arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and liver. The plasma concentration of baloxavir marboxil was very low or below the limit of quantitation (< 0.100 ng/mL).

The pharmacokinetic parameters of baloxavir in Japanese healthy adult subjects after a single oral administration of 40 mg baloxavir marboxil in the fasted and fed states are summarised in Table 8. The pharmacokinetic parameters of baloxavir in Caucasian healthy adult subjects after a single oral administration of 80 mg baloxavir marboxil in the fasted state are summarised in Table 9.

Table 8 Pharmacokinetic parameters of plasma baloxavir in Japanese healthy subjects after a single oral dose of 40 mg baloxavir marboxil in the fasted and fed state

Parameters	Geometric Mean (CV%)	
	Fasted	Fed
N	14	14
C_{max} (ng/mL)	130 (24.1)	67.6 (40.0)
T_{max} (hr) [a]	4.00 (3.00, 5.00)	4.00 (0.50, 5.00)
$AUC_{0\text{-}last}$ (ng·hr/mL)	6932 (19.2)	4406 (38.8)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7086 (19.6)	4540 (39.1)
$t_{1/2,z}$ (hr)	93.9 (21.6)	97.5 (22.8)
CL/F (L/hr)	4.78 (19.6)	7.45 (39.1)
V_z/F (L)	647 (19.1)	1050 (35.6)

[a] Median (Min, Max)

Table 9 Pharmacokinetic parameters of plasma baloxavir in Caucasian healthy subjects after a single oral dose of 80 mg baloxavir marboxil in the fasted state

Parameters	Geometric Mean (CV%)
N	12
C_{max} (ng/mL)	145 (25.4)
$AUC_{0\text{-}last}$ (ng·hr/mL)	6305 (21.2)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6551 (22.5)
$t_{1/2,z}$ (hr)	79.1 (22.4)
CL/F (L/hr)	10.3 (22.5)

Oral drug clearance of baloxavir in the typical Asian and non-Asian patient (65 kg) was respectively 9.3 L/h and 5.4 L/h. In the Phase 3 study in otherwise healthy patients (CAPSTONE-1), mean drug exposure to baloxavir in terms of $AUC_{0\text{-}inf}$ and C_{max} were respectively 6881 ng.hr/mL and 103 ng/mL in the typical Asian patient, and respectively 4645 ng.hr/mL and 70.5 ng/mL in the typical non-Asian patient. There were no differences in pharmacokinetic parameters between influenza patients who are otherwise healthy (CAPSTONE-1) and patients who are at high risk of complications (CAPSTONE-2).

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 and 93.9 hours in Japanese subjects (Tables 8 and 9).

Linearity/non-linearity: Following single oral administration of baloxavir marboxil, baloxavir exhibits linear pharmacokinetics in the fasted state within the dose range of 6 mg to 80 mg.

Absorption

Following a single oral administration of 80 mg of baloxavir marboxil, peak plasma concentration (T_{max}) of baloxavir was reached at approximately 4 hours in the fasted state. The absolute bioavailability of baloxavir marboxil has not been established.

Food effect

A food-effect study involving the administration of baloxavir marboxil 20 mg tablets to healthy volunteers under fasting conditions and with a moderate fat, moderate calorie meal (approximately 400 to 500 kcal including 150 kcal from fat) indicated that the C_{max}, AUC_{0-72} and AUC_{0-inf} of baloxavir were decreased by 48%, 44% and 37%, respectively, under fed conditions. T_{max} was unchanged in the presence of food. In clinical studies with influenza patients where Xofluza was administered with or without food, no clinically relevant differences in efficacy were observed.

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 following a single oral administration of 80 mg of baloxavir marboxil is approximately 1180 litres in Caucasian patients and 647 litres in Japanese subjects.

Metabolism

In vitro studies revealed that arylacetamide deacetylase in the gastrointestinal lumen, intestinal epithelium, and the liver mainly contributes to the conversion from baloxavir marboxil to baloxavir, and baloxavir is primarily metabolised by UGT1A3 with minor contribution from CYP3A4.

In the human mass balance study, after administration of a single oral dose of 40 mg of [^{14}C]-labelled baloxavir marboxil, baloxavir accounted for 82.2% of the plasma AUC for total radioactivity. Baloxavir glucuronide (16.4% of the plasma AUC for total radioactivity) and (12aR,5R,11S) sulfoxide of baloxavir (1.5% of the plasma AUC for total radioactivity) were also detected in plasma.

Excretion

Baloxavir marboxil and baloxavir are excreted mainly via the faecal route in humans. Following a single oral administration of 40 mg of [^{14}C]-labelled baloxavir marboxil, the proportion of total radioactivity excreted was 80.1% in the faeces and 14.7% in the urine. The fraction of administered dose excreted in the urine as baloxavir was 3.3%.

Pharmacokinetics in special populations

Hepatic impairment

Geometric mean ratios (90% confidence interval) of C_{max} and AUC of baloxavir in patients with moderate hepatic impairment (Child-Pugh class B) compared to healthy controls were 0.80 (0.50 – 1.28) and 1.12 (0.78 – 1.61), respectively. Since no clinically meaningful differences in the pharmacokinetics of baloxavir were observed in patients with moderate hepatic impairment (Child-Pugh class B) compared with healthy controls with normal hepatic function, no dose adjustment is required in patients with mild or moderate hepatic impairment.

The pharmacokinetics in patients with severe hepatic impairment has not been evaluated.

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. Renal excretion represents a minor pathway of elimination for baloxavir marboxil and baloxavir. 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. No dose adjustment is required in patients with renal impairment.

Baloxavir is unlikely to be significantly removed by dialysis.

Age

A population pharmacokinetic analysis using plasma baloxavir concentrations from clinical studies with baloxavir marboxil for subjects aged 12 to 64 years did not identify a clinically meaningful effect of age on the pharmacokinetics of baloxavir.

Elderly

Pharmacokinetic data collected in patients ≥ 65 years show that drug exposure to baloxavir was similar to patients aged ≥ 12 to < 64 years.

Paediatrics

The pharmacokinetics of Xofluza in paediatric patients (< 12 years of age) has not been established.

Body weight

Body weight had a significant effect on the pharmacokinetics of baloxavir (as body weight increases, baloxavir exposure decreases). The dose proposed in adults is 40 mg for patients with body weight 40 kg to < 80 kg and 80 mg for patients with body weight ≥ 80 kg. When dosed with the recommended weight-based dosing, no clinically significant difference in exposure was observed between body weight groups.

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, baloxavir exposure is approximately 35% lower in non-Asians as compared to Asians. At the recommended dose, this difference is not considered to be clinically significant and no dose adjustment based on race is required.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Baloxavir marboxil, and its active form, baloxavir, were negative in bacterial reverse mutation tests and micronucleus tests with cultured mammalian cells. Baloxavir marboxil was negative in an *in vivo* rodent micronucleus test.

Carcinogenicity

Carcinogenicity studies have not been performed with baloxavir marboxil.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Croscarmellose sodium
Povidone
Microcrystalline cellulose
Sodium stearylfumarate
Hypromellose
Purified talc
Titanium dioxide

6.2 INCOMPATIBILITIES

Refer to section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. Xofluza should not be used after the expiry date (EXP) shown on the pack.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep in original carton to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Xofluza 20 mg is supplied in aluminium blister packs of 2 film-coated tablets.
Xofluza 40 mg is supplied in aluminium blister packs of 2 film-coated tablets.

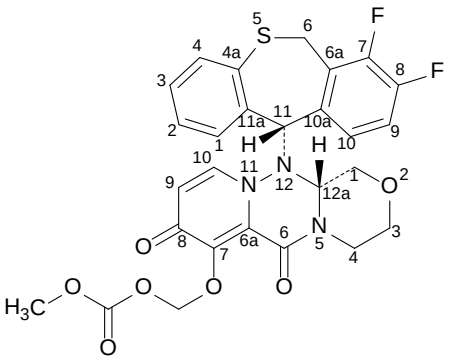
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical structure:



CAS-number: 1985606-14-1

Chemical name: ({(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.

Empirical formula: $C_{27}H_{23}F_2N_3O_7S$.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

21 February 2020

10. DATE OF REVISION

Not applicable

Summary table of changes

Section Changed	Summary of new information