NEW ZEALAND DATA SHEET
Xofluza® Film-Coated Tablets

1. PRODUCT NAME

Xofluza (baloxavir marboxil) 20 mg and 40 mg film-coated tablets.

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

Treatment of influenza

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.

Prophylaxis of Influenza

Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals 12 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Treatment of influenza

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

Prophylaxis of Influenza

A single dose of Xofluza should be taken following close contact with a symptomatic individual.

Dose

Treatment or Post-Exposure Prophylaxis of 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 Single 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

The safety and efficacy of Xofluza for the treatment of influenza in elderly patients age ≥ 65 years and weighing at least 40 kg have been established. No dosage adjustment is recommended in elderly patients (see section 5.2 Pharmacokinetics in special populations, Elderly).

Paediatric population

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

No warnings and precautions based on the available data.

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), substrates or inhibitors of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) enzyme, or gut, renal, or hepatic transporters.

Polyvalent cation containing products may decrease plasma concentrations of baloxavir. Xofluza should not be taken with polyvalent cation containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, magnesium.

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 normal humoral antibody response to infection.

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

Itraconazole, an inhibitor of P-glycoprotein (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 and baloxavir inhibited the efflux transporter (P-gp). Baloxavir, but not baloxavir marboxil, inhibited Breast Cancer Resistance Protein (BCRP).

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, OAT1, 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

Pregnancy

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.

Baloxavir marboxil did not cause malformations in rats or rabbits. High dose levels of baloxavir marboxil given to pregnant rabbits caused maternal toxicity resulting in miscarriages and an increase in the incidence rates of minor skeletal abnormalities in rabbits but no malformations. Such effects were not seen in rats (see section 5.3, Reproductive toxicity).

Labour and delivery

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

Breastfeeding

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.

Fertility

No effects on fertility were observed in animal studies performed with baloxavir marboxil (see section 5.3, Fertility).

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 UNDESIRABLE EFFECTS

Summary of the safety profile

The overall safety profile of Xofluza is based on data from 2483 subjects in 18 clinical trials receiving Xofluza.

Treatment of influenza

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.

Prophylaxis of Influenza

No adverse drug reactions have been identified based on a placebo-controlled clinical study (BLOCKSTONE), in which 374 subjects received Xofluza. The safety profile of Xofluza administered for post-exposure prophylaxis of influenza is comparable to the safety profile established for the treatment of influenza.

Tabulated summary of adverse reactions in clinical trials

No adverse drug reactions have been identified in clinical trials with Xofluza.

Post-marketing experience

The following adverse drug reactions have been identified from post-marketing experience with Xofluza based on spontaneous case reports and cases from non-interventional study programs (Table 2). 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Adverse drug reactions from post-marketing experience

Adverse reaction	**Frequency Category**
Immune system disorders	
Anaphylaxis	Unknown[1]
Anaphylactic reactions	Unknown[1]
Hypersensitivity	Unknown[1]

Adverse reaction	Frequency Category
Skin and subcutaneous disorders	
Urticaria	Uncommon[2]
Angioedema	Unknown[1]

[1] Not observed in clinical trials. As these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

[2] Calculated from frequency of events in completed clinical studies.

Description of selected adverse drug reactions

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 urticaria and angioedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

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.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Direct-acting anti-viral for systemic use; ATC code: J05AX25

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/F/N/S 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

Influenza A virus isolates with treatment-emergent amino acid substitutions in the PA protein at position I38T/F/M/N/S associated with > 10-fold reduced susceptibility to baloxavir and influenza B virus isolates with treatment-emergent amino acid substitutions in the PA protein at position I38T associated with > 5-fold reduced susceptibility to baloxavir were observed in clinical studies. The clinical impact of this reduced susceptibility is unknown.

No pre-treatment isolates, with amino acid substitutions associated with reduced susceptibility to baloxavir, were found in the clinical studies. Prescribers should consider available information from the WHO and/or local government websites on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use Xofluza.

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.

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 efficacy and safety

Treatment of influenza

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.

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 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

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 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: 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).

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 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

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

Virus Subtype: 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 groups.

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.

Prophylaxis of influenza

BLOCKSTONE (Study 1601T0831)

BLOCKSTONE is a phase 3, randomised, double-blind, multicentre, placebo-controlled study designed to evaluate the efficacy of a single oral dose of Xofluza compared with placebo in the prevention of influenza in subjects who are household members of influenza-infected patients. Influenza-infected index patients were required to have onset of symptoms for no

more than 48 hours and subjects were required to have lived with the influenza-infected index patients for > 48 hours.

A total of 749 subjects were randomised and received a single oral dose of Xofluza, according to body weight and age, or placebo, on Day 1. Subjects 12 years of age and over received 40 mg or 80 mg of Xofluza according to body weight (≥ 40 to < 80kg or ≥ 80kg, respectively). Subjects under 12 years of age were dosed according to body weight. The predominant influenza virus strains in the index patients of this study were the A/H3NX subtype (48.4% to 48.8%) and the A/H1N1pdm subtype (47.1% to 48.0%) followed by the B subtype (0.5% to 0.8%) for the household contact groups in the baloxavir marboxil and placebo arms, respectively. 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 between Day 1 and Day 10. Influenza virus positivity was assessed by reverse transcription polymerase chain reaction (RT-PCR), fever was defined as a body temperature (axillary) ≥ 37.5°C, and respiratory symptoms were defined as having a symptom of 'cough' or 'nasal discharge/nasal congestion' with a severity of '2, Moderate' or '3, Severe' as assessed in the subject diary.

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 Xofluza group (Table 8).

Table 8 Proportion of subjects with influenza virus, fever, and at least one respiratory symptom (Xofluza vs Placebo)

Proportion of subjects with influenza virus, fever, and at least one respiratory symptom (%)			
Xofluza (95% CI) N=374	Placebo (95% CI) N=375	Risk Ratio (95% CI for risk ratio)	P-value[2]
1.9 (0.8, 3.8)	13.6 (10.3, 17.5)	0.14 (0.06, 0.30)	< 0.0001

CI = confidence interval

[1] P-value calculated using the modified Poisson regression approach of a binary response

The analysis for the secondary endpoint of proportion of subjects with influenza virus infection (RT-PCR positive regardless of clinical symptoms) in the period from Day 1 to Day 10 demonstrated results consistent with the primary endpoint. There was a reduction in the proportion of subjects with influenza virus infection from 30.4% (95% CI: 25.8, 35.3) in the placebo group to 13.1% (95% CI: 9.9, 16.9) in the Xofluza group.

Prophylaxis of Influenza in subjects ≥ 12 years: The subgroup analysis of the primary endpoint by age revealed the proportion of symptomatic influenza-infected (RT-PCR positive) subjects from Day 1 to Day 10 was lower in the Xofluza group than in the placebo group for subjects 12 years of age and older (1.3% vs. 13.2%, p < 0.0001).

Paediatric population

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

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 9. 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 10.

Table 9 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 10 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)

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 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 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.

Biotransformation

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 metabolized 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, confirming that the *in vivo* metabolism of baloxavir marboxil occurs via ester hydrolysis to form baloxavir with subsequent metabolism of baloxavir to form sulfoxides, and a glucuronide.

Elimination

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%.

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 9 and 10).

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.

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. 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 is identified as the significant covariate based on the population pharmacokinetic analysis. 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.

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, in addition to body weight, race is a covariate on CL/F of baloxavir, however, no dose adjustment based on race is required.

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.

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.

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 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

Reproductive toxicity

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 maternal or fetal toxicity up to the highest tested dose of 1000 mg/kg/day, which is equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

In rabbits, a dose level of 1000 mg/kg/day (equivalent to 12-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. This minor skeletal variation is reabsorbed during the growing process of adjacent cervical vertebra. A dose of 100 mg/kg/day (equivalent to 7-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 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

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

Not applicable.

6.3 SHELF LIFE

The shelf life of the tablets is 5 years.

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 or 4 film-coated tablets.
Xofluza 40 mg is supplied in aluminium blister packs of 1 or 2 film-coated tablets.

Not all pack sizes may be marketed.

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.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

07 October 2021

10. DATE OF REVISION

21December 2023

Summary of Changes Table

Section Changed	Summary of new information
Section 4.5	Addition of '*substrates or*' to provide additional clarity on drug-drug interactions
Section 5.1	Addition of I38S treatment emergent substitution