PROPOSED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 PROPRIETARY NAME AND DOSAGE FORM

Xofluza® 20 mg tablets

Xofluza® 40 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: baloxavir marboxil

20 mg film-coated tablets containing 20 mg baloxavir marboxil

40 mg film-coated tablets containing 40 mg baloxavir marboxil

Excipients with known effect: Lactose monohydrate.

Each 20 mg tablet contains 77,9 mg of lactose monohydrate and 40 mg tablet contains 155,8 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

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".

CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of Influenza

Xofluza is indicated for the treatment of influenza in patients aged 12 and above who have been symptomatic for no more than 48 hours.

Xofluza is indicated for treatment of uncomplicated influenza in patients aged 12 years and above who have been symptomatic for no more than 48 hours, and are at high risk of developing influenza complications.

Post- exposure prophylaxis of Influenza

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

4.2 Posology and method of administration

Method of Administration

Xofluza may be taken with or without food (see 5.1).

However, co-administration of Xofluza with dairy products and polyvalent cation containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, magnesium should be avoided (see 4.5)

Treatment of Influenza.

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

Post-exposure prophylaxis of Influenza

A single dose of Xofluza should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza.

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

Table 1

Patient Body Weight (kg)	Recommended Single Oral Dose
40 kg to < 80 kg	40 mg
80 kg	80 mg

Dose Modifications

No dose reductions of Xofluza are recommended

Elderly use

No dosage adjustment is recommended (see section 5.2).

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).

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).

Xofluza has not been studied in patients with severe hepatic impairment.

4.3 Contraindications

Xofluza is contraindicated in patients with a known hypersensitivity to baloxavir marboxil or any of the excipients in Xofluza.

4.4 Special warnings and precautions for use

General

No warnings and precautions based on the available data.

Sugar

Xofluza contains lactose. Patients with the rare hereditary conditions of galactose intolerance lactase deficiency, glucose-galactose malabsorption intolerance should not take Xofluza.

Xofluza contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

No clinically significant 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 UDP-glucuronosyltransferasHe (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.

Effects of Other medicines on Baloxavir Marboxil or its Active Metabolite

Baloxavir

Itraconazole, an inhibitor of P-gp, increased the Cmax 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 Cmax 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 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 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 medicines 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 medicines that are substrates of P-gp.
A single 80 mg dose of baloxavir marboxil decreased Cmax and AUC0-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

Xofluza should be avoided during pregnancy.The potential risk of Xofluza in pregnant women is unknown.

Xofluza given to pregnant rabbits caused maternal toxicity resulting in miscarriages and an increase in the incidence of skeletal abnormalities.

Breastfeeding/Lactation

The safety of Xofluza during lactation has not been established. Use of Xofluza during lactation is not recommended. 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.

Labour and Delivery

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

Fertility

No effects on fertility were observed in animal studies performed with Xofluza.

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

Clinical Trials

The overall safety profile of Xofluza is based on data from 2 483 subjects in 18 clinical trials receiving Xofluza.

Treatment of influenza

No adverse drug reactions were observed on pooled data from 3 placebo controlled clinical studies (studies 1518T0821, 1601T0831and 1602T0832) in adult and adolescent patients, in which a total of 1 640 patients received Xofluza.

This included 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.1 334 patients (81,3 %) were
adults ≥ 18 years to ≤ 64 years, 209 patients (12,7 %) were adults ≥ 65 years and 97 patients (5,9 %) were adolescents (≥ 12 years to < 18 years). Of these, 1 440
patients received Xofluza at 40 mg and 80 mg doses and 100 patients each received 10 mg or 20 mg doses. The safety profile in patients at high risk was similar to that in otherwise healthy adults and adolescents

Post-exposure prophylaxis of Influenza

No adverse drug reactions have been identified based on a placebo-controlled clinical study (study 1719T0834), in which a total of 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

Table 2 Incidence of adverse events occurring in ≥ 1 % of subjects

receiving Xofluza in the acute uncomplicated influenza trials

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

Post marketing experience

The following adverse drug reactions have been identified from postmarketing Experience with baloxavir marboxil (Table 3) based on spontaneous case reports and cases from non-interventional study programs. 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.

Table 3 Adverse drug reactions from post marketing experience

Adverse reactions	Frequency Category
Anaphylaxis	Unknown[1]
Anaphylactic reactions	Unknown[1]
Hypersensitivity	Unknown[1]
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.

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.

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 to SAHPRA via he 6.04 Adverse Drug Reaction Report Form , found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Clinical experience

Reports of overdoses with Xofluza have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported. Whilst a limited number of cases of overdose have been reported in association 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral agents, 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. The 50% inhibition concentration (IC50) 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 (EC50) values of baloxavir were 0,73 nmol/L (n=31; range: 0,20-1,85 nmol/) 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 a MDCK cell-based virus titre reduction assay, the 90 % effective concentration (EC90) 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. At twice the expected exposure from recommended dosing, Xofluza did not prolong the QTc interval.

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 4. 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 5.

Table 4 Pharmacokinetic parameters of plasma baloxavir in Japanese healthy subjects after administration of 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/m)	130 (24,1)	67,6 (40,0)
T_{max} [a] (hr)	4,00 (3,00, 5,00)	4,00 (0,50, 5,00)
$AUC_{0\text{-las}}$ (ng hr/m)	6 932 (19,2)	4 406 (38,8)
$AUC_{0\text{-inf}}$ (ng hr/m)	7 086 (19,6)	4 540 (39,1)
$t_{1/2,}$ (hr)	93,9 (21,6)	97,5 (22,8)
CL/F (/hr)	4,78 (19,6)	7,45 (39,1)
V_z /F ( )	647 (19,1)	1 050 (35,6)

a Median (Min, Max)

Table 5: Pharmacokinetic parameters of plasma baloxavir in Caucasian healthy subjects after administration of a single oral dose of 80 mg of baloxavir marboxil in the fasted state (Study 1612T081C)

Parameters	**Geometric Mean (CV %)**
N	12

Cmax (ng/mL)	145 (25,4)
$AUC_{0\text{-las}}$ (ng hr/mL)	6 305 (21,2)
$AUC_{0\text{-inf}}$ (ng hr/mL)	6 551 (22,5)
t1/2,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 baloxavir marboxil 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 approximately 1 180 L in Caucasian patients and 647 L 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 40mg of [14C]-labeled 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.

Excretion

Baloxavir marboxil and baloxavir were 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 in faeces was 80,1 % of the administered dose and 14,7% was excreted in urine. The amount of baloxavir excreted in the urine was 3,3 % of the administered dose.

Elimination

The apparent terminal elimination half-life (t1/2,z) of baloxavir after a single oral administration of baloxavir marboxil is 79,1 hours in Caucasian patients, and 93,9 hours in Japanese subjects, see Tables 1 and 2.

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

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, race is a covariate on 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 with baloxavir marboxil for subjects aged 12 to 64 years did not identify a clinically meaningful effect of age on the pharmacokinetics of baloxavir.

Paediatric Population

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

Elderly Population

Pharmacokinetic data collected in patients ≥ 65 years show that exposure to baloxavir was similar to patients aged ≥ 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. Renal excretion represents a minor
pathway of elimination for baloxavir marboxil or 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.

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.

Summary of clinical studies

Treatment of Influenza

Otherwise healthy patients

Study 1601T0831

Study 1601T0831 is a randomised, double-blind, multicentre, placebo- and active-controlled study designed to evaluate the efficacy and safety of single oral dose of baloxavir compared with placebo or oseltamivir in otherwise healthy adult and adolescent patients (aged ≥ 12 years to ≤ 64 years) with influenza.

A total of 1 436 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 baloxavir according to weight (< 80 kg or 80 kg respectively), oseltamivir 75 mg twice daily for 5 days (if aged > 20 years) or placebo. 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 baloxavir when compared with placebo, see Table 6.

Table 6 Time alleviation of symptoms in otherwise healthy patients with influenza (baloxavir vs placebo)

Time to Alleviation of Symptoms (Median [hours])			
Baloxavir 40/80 mg (95 % CI) N=455	Placebo (95 % CI) N=230	Difference between Baloxavir 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

When the baloxavir group was compared to the oseltamivir group, there was no statistically significant difference in time to alleviation of symptoms (53,5 h s 53,8 h respectively), see Table 7.

Table 7 Time to alleviation of symptoms in otherwise healthy patients with influenza (≥ 20 years of age), (Baloxavir vs Oseltamivir)

Time to Alleviation of Symptoms (Median [hours])			
Baloxavir 40/80 mg (95 % CI) N=375	Oseltamivir (95 % CI) N=377	Difference between Baloxavir and Oseltamivir (95 % CI for difference)	P-value
53,5 (48,0, 58,5)	53,8 (50,2, 56,4)	-0,3 (6,6, 6,6)	0,7560

CI: Confidence intervaL

Secondary endpoints included time to resolution of fever and culture-based assessment of time to cessation of viral shedding (by virus titre).

Resolution of fever

Following study medicine administration there was faster resolution of fever in the baloxavir group compared with the placebo group. The median time to resolution of fever in patients treated with baloxavir 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 group compared with the oseltamivir group.

Antiviral Activity

Patients treated with baloxavir 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 baloxavir group compared with 72 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 baloxavir 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 baloxavir (10, 20 or 40 mg) or placebo in the 2015-2016 Northern Hemisphere influenza season in Japan. The predominant influenza virus strain as 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) in the baloxavir group versus 77,7 hours (96 % 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 study 1601T0831.

Study 1602T0832

Study 1602T0832 is a randomised, double-blind, multicentre, placebo- and active controlled study designed to evaluate the efficacy and safety of single oral dose of baloxavir 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 2 184 patients were randomised to receive a single oral dose of 40 mg or 80 mg of baloxavir according to body weight 40 to < 80kg or ≥ 80kg respectively), oseltamivir 75 mg twice daily for 5 days, or placebo. 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 baloxavir when compared with placebo, see Table 8.

Time to Improvement of Influenza Symptoms (Baloxavir vs Placebo)

Time to Improvement of Influenza Symptoms (Median [hours])			
Baloxavir 40/80 mg (95 % CI) N=385	***Placebo (95 % CI) N=385***	***Difference between Baloxavir 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 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), see Table 9.

Table 9 Time to Improvement of Influenza Symptoms (Baloxavir vs Oseltamivir)

Time to Improvement of Influenza Symptoms (Median hours)			
Baloxavir 40/80 mg (95 % CI) N=385	Oseltamivir (95 % CI) N=388	Difference between Baloxavir and Oseltamivir (95 % CI for difference)	P-value
73,2 (67,5, 85,1)	81,0 (69,4, 91,5)	-7,7 (−22,7, 7,9)	0.8347

Virus Subtype

For patients infected with type A/H3 virus (predominant strain), the median time to improvement of influenza symptoms was statistically significantly shorter in the baloxavir group compared with the placebo group but not compared with the oseltamivir group (see Table 9). In the subgroup of patients infected with type B virus, the median time to improvement of influenza symptoms was statistically significantly shorter in the baloxavir group compared with both the placebo and oseltamivir group.

Table 10 Time to Improvement of Symptoms by Influenza Virus Subtype

Time to Improvement of Symptoms (Hours) Median [95 % CI]			
Virus	Baloxavir	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

Resolution of Fever

The proportion of patients who had fever was reduced more rapidly in the baloxavir group than in the placebo group following study medicine administration. The median time to resolution of fever was 30,8 hours (95 % CI: 28,2, 35,4) in the baloxavir group compared with 50,7 hours (95 % CI: 44,6, 58,8) in the placebo group. No significant differences between the baloxavir 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 baloxavir

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 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).

The proportion of patients requiring systemic antibiotics for infections secondary to influenza infection was lower in the baloxavir 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 baloxavir group was comparable with the proportion in the oseltamivir group (3,9 %).

Antiviral Activity

Patients at high risk of influenza complications, treated with baloxavir, 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 baloxavir group compared with 96 hours in the placebo group and the oseltamivir group.

Post-exposure prophylaxis of influenza

Study 1719T0834

Study 1719T0834 was a phase 3, randomised, double-blind, multicenter, 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 ≤ 48 hours and subjects were required to have lived with the influenza-infected index patients for > 48 hours.

A total of 749 subjects were randomized 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 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%) according to household contact groups Xofluza and placebo, 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 in the period from Day 1 to 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 baloxavir marboxil group (see Table 11) .

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	N=375 13.6	 0.14	< 0.0001

(0.8, 3.8)	(10.3, 17.5)	(0.06, 0.30)	
Proportion of Subjects ≥ 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

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 baloxavir marboxil group.

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 unknown.

No pre-treatment isolates, with amino acid substitutions associated with reduced susceptibility to baloxavir, were found in the clinical studies or in the National Centre for Biotechnology Information/Influenza virus resources database. Medical practitioners should consider available information from the National Institute

for Communicable Diseases (NICD) on influenza virus susceptibility patterns and treatment effects when deciding whether to use baloxavir.

In the phase 3 study in otherwise healthy patients (1601T0831), PA/I38T/M were detected in 36 of 370 patients in the baloxavir treatment group. In the phase 3 study in high risk patients (1602T0832), PA/I38T/M/N were detected in 15 of 290 patients in the baloxavir 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.

Immunogenicity

Immune Response

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients - Core: croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, povidone K25, and sodium stearyl fumarate.

Excipients Film coat: hypromellose, talc and titanium dioxide (E171).

Contains sugar (lactose monohydrate)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store tablets at or below 30 °C

Store blister in outer carton until required for use, in order to protect from moisture and light.

Store out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

20 mg tablets: Aluminium blister packs containing 2 or 4 tablets.

40 mg tablets: Aluminium blister packs containing 1 or 2 tablets.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Disposal of unused/expired medicines

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. Use established collection systems, if available in your location.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

24 Fricker Road

Illovo

Gauteng

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Xofluza 20 mg: 55/20.2.8/0333

Xofluza 40 mg: 55/20.2.8/0334

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 09 February 2021

10. DATE OF REVISION OF THE TEXT

Last revision: 02 August 2022