Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Baloxavir marboxil

Proprietary Product Name: Xofluza

Sponsor: Roche Products Pty Limited

June 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
AGEP	Acute generalised exanthematous pustulosis
ASA	Australian specific Annex
AUC	Area under the concentration-time curve
$AUC_{0\text{-}72}$	Area under the plasma concentration-time curve from time 0 to 72 hours
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve extrapolated from time zero to infinity
BE	Bioequivalence
BID	Twice daily
Bxm	Baloxavir marboxil
C24	Plasma concentration 24 hours after dosing
C96	Plasma concentration 96 hours after dosing
CDC	Centers for Disease Control and Prevention (United States)
CEN	Cap-dependent endonuclease
CI	Confidence interval
CL/F	Apparent total clearance
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLP	Data lock point
EC_{50}	Half maximal effective concentration
FDA	Food and Drug Administration (United States)
GVP	Good Pharmacovigilance Practice(s)
HR	High risk

Abbreviation	Meaning
ITTI	Intention-to-treat infected
M2	Matrix-2 ion-channel
NAI	Neuraminidase inhibitor
OwH	Otherwise healthy (patients)
PA	Polymerase acidic protein
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PPS	Per protocol set
PSUR	Periodic safety update report
QTc	Corrected QT interval
RAS	Resistance-associated substitutions
RMP	Risk management plan
RNA	Ribonucleic acid
S-033188	Baloxavir marboxil (drug development name)
SAE	Serious adverse event
SJS	Stevens–Johnson syndrome
T_{max}	Time to maximum plasma concentration
TTAS	Time to alleviation of symptoms
TTIS	Time to improvement of symptoms
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Apparent volume of distribution based on the terminal phase

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	21 February 2020
Date of entry onto ARTG:	21 February 2020
ARTG numbers:	317240, 317241
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Baloxavir marboxil
Product name:	Xofluza
Sponsor's name and address:	Roche Products Pty Limited 30-34 Hickson Road, Sydney NSW 2000
Dose form:	Film coated tablet
Strengths:	20 mg, 40 mg
Container:	Blister pack
Pack size:	2
Approved therapeutic use:	*Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 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.*
Route of administration:	Oral
Dosage:	A single oral dose of Xofluza should be taken within 48 hours of symptom onset. *Adults and Adolescents (≥ 12 years of age)* The recommended dose of Xofluza depending on body weight is: • 40 kg to < 80 kg: 40 mg. • ≥ 80 kg: 80 mg For further information on dosage, refer to the Product Information.

Product background

This AusPAR describes the application by Roche Products Pty Limited (the sponsor) to register Xofluza (baloxavir marboxil) 20 mg and 40 mg film coated tablets for the following proposed indication:

> *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 the treatment of influenza in patients aged 12 and above who have been symptomatic for no more than 48 hours, and are at high risk of developing influenza complications.*

Influenza is an acute and usually self-limiting respiratory infection caused by the influenza A and B virus. Influenza is spread via airborne droplets and it is highly contagious. The incubation period is typically one to four days and characteristically has a rapid onset. Typical symptoms are high fever, chills, headache, muscle pains and loss of appetite. Respiratory symptoms typically include cough, sore throat and nasal congestion. Severe complications of influenza include primary viral pneumonia, leading to respiratory failure and death; superimposed bacterial infection such as bronchitis, sinus, and otitis media; and decompensation of underlying diseases such as asthma, other chronic lung diseases, and congestive cardiac failure. Hospitalisations and deaths can occur at any age but most occur in children under five years of age and in the elderly.

Influenza typically occurs as winter epidemics in temperate climates but endemically in tropical climates with more limited outbreaks year round. In Australia, epidemics occur mainly during winter in temperate regions, while the pattern of infection in sub-tropical and tropical regions is less predictable. Episodic pandemics may result in millions of severe cases worldwide with up to 650,000 deaths every year. In Australia, influenza causes approximately 100 deaths and 5100 hospitalisations annually although these are likely to be significantly under-reported. Mathematical modelling suggests that there are more than 3000 deaths and more than 13,500 hospitalisations annually due to influenza in Australians aged more than 50 years.[1] The incidence and severity of epidemics and pandemics is dependent in part on the effectiveness of vaccines to new emerging viral strains.

In Australia, the National Influenza Surveillance Scheme monitors the incidence and prevalence of influenza and is responsible for pandemic planning. Prevention of influenza through vaccination programs is the most effective way of controlling the disease. In Australia, vaccination is widely available and is recommended for anyone aged six months or older, and is funded by the National Immunisation Program for high risk patients, including the elderly. Treatment with antiviral drugs is not recommended as a substitute for vaccination but as an option if vaccination is ineffective or unavailable. Vaccines take months to manufacture and rapid antigen shifts may limit effectiveness. In addition, vaccination is contraindicated in some patients. In Australia, the matrix-2 (M2) ion-channel blocker amantadine is registered but not recommended due to widespread transmissible resistance. Neuraminidase inhibitors (NAI; oseltamivir, zanamivir and peramivir) are registered in Australia. NAIs are effective but they form a single class which may become vulnerable to a highly mutable virus. Oseltamivir and zanamivir are taken orally twice daily (BID) for five days, and peramivir is given intravenously (IV) as a single dose.

Baloxavir marboxil is a new class of antiviral agent with a novel mechanism of action. It acts on cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic protein (PA) subunit of the viral ribonucleic acid (RNA) polymerase

[1] Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2018, immunisationhandbook.health.gov.au.

complex. It inhibits the transcription of influenza virus genomes resulting in the inhibition of influenza virus replication. Cross-resistance with baloxavir marboxil and other anti-influenza drugs is not expected, and effectiveness against strains with resistance to NAIs is anticipated. The sponsor proposes that baloxavir marboxil will be an effective, alternative option to the NAIs with the advantage of a single oral dose.

This application was evaluated as part of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium, with work-sharing between the TGA, Health Canada and Swissmedic.[2] Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

Xofluza (baloxavir marboxil) is considered a new chemical entity for Australian regulatory purposes.

Baloxavir marboxil was first approved in Japan for the treatment of influenza A or B virus infection in otherwise healthy (OwH) patients in February 2018. Baloxavir marboxil was approved in October 2018 in the United States (US), in February 2019 in Hong Kong, and in March 2019 in Thailand for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. In addition, baloxavir marboxil was also approved on 28 March 2019 in Thailand for the treatment of influenza in patients aged 12 and above who have been symptomatic for no more than 48 hours, and are at high risk of developing influenza complications.

The application for high risk patients was also submitted to the US Food and Drug Administration (FDA). The indication for patients at high risk of developing influenza-related complications was approved by the FDA on 17 October 2019. The FDA approved indications are as follows:

> *Xofluza is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and who are:*
>
> - *otherwise healthy, or*
> - *at high risk of developing influenza-related complications[1] (see Clinical Studies (14.2))*
>
> *Limitations of Use: Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use Xofluza (see Microbiology (12.4) and Clinical Studies (14)).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[2] The ACSS Consortium is a medium-sized coalition, which was formed in 2007 by 'like-minded' regulatory authorities to promote greater regulatory collaboration and alignment of regulatory requirements. Its goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products. For further information, visit the relevant TGA webpage: https://www.tga.gov.au/australia-canada-singapore-switzerland-acss-consortium.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2019-01386-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2019
First round evaluation completed	27 September 2019
Sponsor provides responses on questions raised in first round evaluation	28 October 2019
Second round evaluation completed	23 December 2019
Delegate's Overall benefit-risk assessment	28 November 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	21 February 2020
Completion of administrative activities and registration on the ARTG	21 February 2020
Number of working days from submission dossier acceptance to registration decision*	161

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in TGA's Delegate's overview, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The following points were summarised from the quality evaluation:

- The administrative, product usage, chemical, pharmaceutical, and biopharmaceutic data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

- The proposed product is an immediate release film coated tablet, to be supplied as a 2 and 4 tablet pack for the 20 mg strength, and a 1 and 2 tablet pack for the 40 mg strength.[3] Xofluza is a single use drug and is not intended for chronic use. The maximum daily dose is 80 mg.
- The drug products are immediate release, film coated tablets containing 20 mg and 40 mg of baloxavir marboxil. The tablet cores are compositionally directly proportional (that is, the 40 mg core contains exactly twice the quantity of ingredients as the 20 mg core) and may be manufactured from a common blend. Both strengths are coated with a non-functional white film-coating.
- The tablets are packaged in oriented polyamide/aluminium foil/polyvinyl chloride laminate blisters. The drug product is manufactured via wet-granulation followed by compression. The manufacturing process is well described and controlled.
- The proposed specifications appropriately control identity, assay, related substances, uniformity of dosage units, dissolution and other physical, chemical and microbiological properties relevant to the product.
- Appropriate validation data have been submitted in support of the test procedures.
- Stability data have been generated under stressed, accelerated and real time conditions to characterise the stability profile of the product. No substantial changes are observed to any parameter on storage and the submitted data support a shelf life of 36 months when stored at or below 30°C.
- In terms of food effect, the pivotal Phase III clinical studies used 20 mg tablets only; the 40 mg tablets were not used. The formulation of the 20 mg tablet was the same as that proposed for commercial supply. The 40 mg tablet is directly proportional to the 20 mg tablet. The following studies were considered:
  - Study 1512T0813 (CV40804): a Phase I study to evaluate the relative bioavailability of S-033188 (baloxavir marboxil) 20 mg tablets and suspension and the effect of food on the pharmacokinetics (PK) in healthy adult subjects.
  - Study 1622T081F: a Phase I study to evaluate the bioequivalence (BE) of S-033188 10 mg and 20 mg tablets and effect of food on the pharmacokinetics in healthy adults.
- A bio-waiver has been granted for the 40 mg tablets based on core composition (directly proportional), comparable *in vitro* dissolution data and, linear PK (stated within the dose range of 6 mg to 80 mg (fasted state)).
- The Study 1512T0813 was assessed in detail and there were no concerns regarding the study design, analytical methods or analytical outcomes. The effect of a moderate fat, moderate calorie (approximately 400 to 500 kcal including 150 kcal from fat) meal on a 20 mg dose of baloxavir marboxil was:
  - Decrease in area under the plasma concentration-time curve from time 0 to 72 hours (AUC_{0-72}) and maximum plasma concentration (C_{max}) by approximately 44% and 48%, respectively, when administered with a meal compared to administration under fasting conditions.
  - Decrease in AUC_{0-72} and C_{max} by approximately 48% and 49%, respectively, when administered prior to a moderate fat/calorie meal compared to administration under fasting conditions.
- Similar reductions were observed to the 40 mg dose (Study 1622T081F).

[3] The final registered pack sizes are 2 tablet packs of 20 mg and 40 mg.

- The proposed PI states:

  'Xofluza can be taken with or without food (4.2 Dose and Method of Administration)' and;

  '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. Time to maximum plasma concentration (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.*'

Conclusion from the quality evaluation

Registration is recommended with respect to chemistry and quality control aspects. Biopharmaceutic aspects noted above (food effect) have been brought to the attention of the Delegate.

Nonclinical

The following points were summarised from the nonclinical evaluation:

- The *in vitro* and *in vivo* pharmacology studies support the proposed mechanism of action of baloxavir and indicate that baloxavir has antiviral activity against a broad panel of influenza A and B viruses.
- In toxicity studies in rats and monkeys with daily dosing for up to one month, the main target organ for toxicity is liver. Hepatotoxicity was characterised by increases in liver enzymes in rats and monkeys and increases in liver weight and pathological changes in rats. However, the risk of hepatotoxicity in human is considered low as only single dose administration of baloxavir marboxil is intended clinically. Occasional gastrointestinal adverse findings (loose stool, diarrhoea and/or vomiting) were seen in both species.
- Baloxavir marboxil and baloxavir were tested negative for genotoxicity (*in vitro* and *in vivo*). Carcinogenicity studies were not needed considering single dose treatment.
- Baloxavir marboxil did not affect female or male fertility in rats. Embryofetal development studies (at animal/human exposure ratios 2.1 and ≥ 2.7 fold in rats and rabbits, respectively) showed a decrease in maternal body weight in rats and rabbits and two abortions in rabbits at the highest dose (exposure ratio 6.1). Skeletal variations (increased incidence of cervical ribs and a low incidence of full supernumerary ribs) were increased in high dose rabbits (exposure ratio 6.1). There were no malformations observed. There were no adverse effects of baloxavir marboxil on the overall growth and development of juvenile rats at the clinically relevant exposure. Overall, safety margins were low, but acceptable considering single dose treatment in humans. Pregnancy Category B3 is considered appropriate.[4]

[4] Australian Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Conclusion from the nonclinical evaluation

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Xofluza with the new active substance baloxavir marboxil for the proposed indication.

The draft PI should be amended as directed. It is noted that relevant revisions have been recommended for Section 4.5, 4.6, 5.1, 5.2, and 5.3 of the proposed PI.

Clinical

To support this application, the sponsor has provided 16 PK/pharmacodynamic (PD) studies and the following four safety and efficacy studies:

- Study 1601T0831: a Phase III study in otherwise healthy subjects.
- Study 1601T0832: a Phase III study in subjects who are at high risk of influenza complications.
- Study 1518T0821: a Phase III study in otherwise healthy subjects.
- Study 1518T0822: an open label, Phase III study in paediatric subjects.

Clinical pharmacology

Among the submitted 16 PK/PD studies, 15 studies provided PK data and 3 studies provided PD data. A single dedicated population PK study (popPK) was also included as part of the submission.

The clinical evaluator concluded that the statements in the proposed PI are supported by the submitted data with some PI amendments recommended to more accurately reflect the submitted data.

The following is a brief summary of the results from these studies.

Absorption, distribution, metabolism and excretion

- Following a single dose of the proposed marketing formulation of 20 mg baloxavir marboxil tablets, the median T_{max} value was 4.0 hours.
- Following a single dose of 20 mg tablet or 20 mg suspension of baloxavir marboxil in the fasted state to healthy subjects, the two formulations have similar oral bioavailability.
- *In vitro* dissolution testing indicated that the proposed marketing 20 mg film coated tablet formulation and the 20 mg film coated tablet formulation for clinical use were comparable.
- The sponsor has submitted a request for a biowaiver for conducting a BE study that compares the proposed marketing 40 mg tablet with the proposed marketing 20 mg tablet. Based on the data submitted by the sponsor, a biowaiver appears to be justified in this case.
- 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 C_{max}, AUC_{0-72} and area under the plasma concentration-time curve extrapolated from time zero to infinity (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.

- Following ascending doses of baloxavir marboxil suspension ranging from 6 to 80 mg in healthy adult Asian males in the fasted state baloxavir exposures increased in an almost dose-proportional manner.
- The Thorough QT/corrected QT interval (QTc);[5] study identified that baloxavir exposure increased linearly with dose following doses of 40 mg and 80 mg.
- Following a single oral dose of 20 mg baloxavir marboxil to healthy Asian males, the apparent volume of distribution based on the terminal phase (Vz/F) was 698 L.
- Protein binding ratios ranged from 92.95 to 93.9% with baloxavir primarily bound to albumin.
- Baloxavir marboxil is hydrolysed by a serine esterase in the small intestine, blood and liver to become baloxavir. Metabolism of baloxavir into baloxavir glucuronide was predominantly mediated by uridine 5'diphospho-glucuronosyltransferase family 1 member A3 (UGT1A3), whereas, the formation of the baloxavir sulphoxides was found to be mediated by cytochrome P450 3A4 (CYP3A4).
- The primary metabolite of baloxavir marboxil was baloxavir, which accounted for 82.2% of total radioactivity in plasma. The other metabolites were baloxavir glucuronide and (12a*R*, 5*R*, 11*S*)- baloxavir sulphoxide, which accounted for 16.4% and 1.5%, respectively, of total radioactivity.
- Over a 432 hour collection period, 80% of the radioactivity following a single 40 mg dose of [^{14}C]-baloxavir marboxil was recovered in the faeces, while a further 14.7% was recovered in the urine and the estimated apparent total clearance (CL/F) of baloxavir was 8.83 L/h, whereas, the estimated renal clearance (CL_R) was 0.30 L/h.

Pharmacokinetics in the target population

- Baloxavir plasma concentration 24 hours after dosing (C24), plasma concentration 96 hours after dosing (C96) and Bayesian-estimated exposure indices (C_{max}, $AUC_{0\text{-}inf}$, C24, C72 and C96) were 34% to 48% lower for Non-Asian patients than Asian patients.
- The high-risk categories: asthma or chronic lung disease; endocrine disorders; heart disease; elderly (≥ 65) and morbidity had little effect on the observed baloxavir C24 and C96 values or the Bayesian estimated PK parameters. By contrast, the C24, C96 and Bayesian-estimated exposure indices were 24% to 43% higher for patients with metabolic disorders than those without metabolic disorders.
- Dose normalised baloxavir exposure was lower (31%) in subjects weighing ≥ 80 kg compared to subjects with body weights < 80 kg.
- There appeared to be less of a food effect on baloxavir exposure in the target population.
- The C24 and C96 values appeared to be lower in those < 18 years than in the other age groups.
- The virus type (influenza A or B virus) appeared to have little effect on the observed baloxavir C24 and C96 values.
- Moderate hepatic impairment was associated with a 20% decrease in peak exposure and an increase of 10 to 12% in total exposure.

[5] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

Drug-drug interactions

- A drug-drug interaction (DDI) existed between itraconazole and baloxavir marboxil, whereby exposure to baloxavir is increased by up to 32% when the two drugs are co-administered.
- When co-administered with probenecid, there was a 21% to 25% decrease in baloxavir exposure compared to when baloxavir marboxil was administered alone.
- Digoxin exposure was reduced by about 15% following co-administration with baloxavir marboxil.
- Rosuvastatin C_{max} and AUC decreased by about 15 to 18% following co-administration with baloxavir.
- Co-administration of baloxavir marboxil had no effect on the PKs of midazolam, oseltamivir or oseltamivir carboxylate.

Population pharmacokinetic analysis

PopPK analysis indicated that baloxavir plasma concentrations could be adequately described by a 2-compartment model with first order absorption and absorption lag time. Analysis of PK parameters calculated *post-hoc* by determining empirical Bayesian estimations indicated the following:

- Baloxavir exposures for Non-Asian were lower than those for Asian.
- Baloxavir exposures decrease as body weight increase.
- Baloxavir exposures were similar in adults and adolescents.
- In the Phase II and Phase III studies, administration of baloxavir marboxil with food had little to no effect on *post-hoc* PK parameters for baloxavir when compared to administration in the fasted state or when administered 2 to 4 hours before or after a meal.

Clinical efficacy

The clinical data to support the indication in otherwise healthy (OwH) subjects include one pivotal Phase III study (Study 1601T0831) and one supportive Phase II study (Study 1518T0821). The clinical data to support the indication in high risk (HR) patients is based on one pivotal Phase III study (Study 1601T0832).

The OwH studies (Studies 1601T0831 and 1518T0821) generally excluded patients with HR factors for developing influenza complications, whereas the HR study (Study 1601T0832) required patients to have at least one HR factor. The US Centers for Disease Control and Prevention (CDC) provides a complete list of people at HR of developing flu-related complications.[6] These complications include influenza pneumonia, secondary bacterial pneumonia, bronchitis, sinus and ear infections, hospitalisation, and death. Influenza is also considered to make some chronic health conditions worse, such as asthma and congestive heart failure.

Study 1601T0831 in otherwise healthy subjects

Study 1601T0831 was a randomised, double blind, multicentre, placebo and active controlled Phase III study. The study evaluated the efficacy and safety of baloxavir marboxil (S-033188) in OwH patients aged 12 to 64 years with acute uncomplicated influenza. Key exclusion criteria include patients requiring inpatient treatment. Adult

[6] Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD), People at High Risk for Flu Complications, Accessed from the CDC website, last reviewed 27 August 2018.

patients (20 to 64 years of age) were randomised in a 2:1:2 ratio to receive baloxavir marboxil (single dose on Day 1), placebo, or oseltamivir (75 mg BID for 5 days). Adolescent patients (12 to 19 years of age) were randomized in a 2:1 ratio to receive either baloxavir marboxil or placebo. Baloxavir marboxil dosing was based on the patient's body weight: patients who weighed 40 to 80 kg received 40 mg and patients who weighed 80 kg received 80 mg.

Oseltamivir was not administered to patients under 20 years of age due to a labelling restriction on its use in adolescents in Japan at the time of the study. In each age group, patients were also stratified by region (Japan/Asia or Rest of the World), body weight, and composite influenza symptom score at Baseline. The study drugs were administered at the study centre within 48 hours of the onset of symptoms and without regard to food.

The primary efficacy objective was to evaluate the efficacy of a single dose of baloxavir marboxil compared with placebo by measuring the time to alleviation of symptoms in patients with uncomplicated influenza virus infection. The primary efficacy endpoint is the time to alleviation of symptoms which was defined as the time from the start of treatment to the alleviation of influenza symptoms.

The primary and the secondary analyses were performed in a hierarchical manner to maintain control of overall Type I error. A total of 1436 patients were randomised: 612 patients in the baloxavir marboxil (S-033188) group, 514 patients in the oseltamivir group and 310 patients in the placebo group. 1366 patients completed the study: 578 patients (94.4%) in the baloxavir marboxil (S-033188) group, 498 patients (96.9%) in the oseltamivir group and 290 patients (93.5%) in the placebo group. The proportion of the patients who completed the study was similar among groups.

Results of primary efficacy endpoint

The median time to alleviation of symptoms was 53.7 hours (95% confidence interval (CI): 49.5, 58.5) in the baloxavir marboxil group compared with 80.2 hours (95% CI: 72.6, 87.1) in the placebo group. The difference in median time was -26.5 hours (95% CI: -35.8, -17.8) between the baloxavir marboxil group and the placebo group. The baloxavir marboxil group showed a statistically significantly greater reduction in the time to alleviation of symptoms (TTAS) compared to the placebo group ($p < 0.0001$). Study 1601T0831 has met its primary endpoint as a clinically meaningful and statistically significant reduction in TTAS was observed in the baloxavir marboxil group compared with the placebo group.

In the secondary comparison between baloxavir marboxil and oseltamivir in the 20 to 64 years of age stratum, the median time to alleviation of symptoms was 53.5 hours (95% CI: 48.0, 58.5) in the baloxavir marboxil group compared with 53.8 hours (95% CI: 50.2, 56.4) in the oseltamivir group. The difference in the median time was -0.3 hours (95% CI: -6.6, 6.6) and this was not statistically significant ($p = 0.756$). Similar results were obtained in the per-protocol population.

Table 2: Study 1601T0831 time to alleviation of symptoms (primary efficacy endpoint)

Time to alleviation of symptoms	S-033188 N = 455	Placebo N = 230
Median (hours) (95%CI)	53.7 (49.5, 58.5)	80.2 (72.6, 87.1)
Difference (hours)	-26.5	
P value	<0.0001	
	S-033188 (≥20 years old) N = 375	Oseltamivir N = 377
Median (hours) (95%CI)	53.5 (48, 58.5)	53.8 (50.2, 56.4)
Difference	-0.3	
P value	0.756	

S-033188 is baloxavir marboxil

There were multiple secondary endpoints. The results of key secondary efficacy endpoints were supportive of the primary endpoint results, generally showing beneficial effects of baloxavir marboxil compared with placebo and, in patients aged 20 to 64 years, similar effects compared with oseltamivir. Viral subtype analysis was of limited value since the majority of patients in this study had the influenza A/H3 subtype (84.8% to 88.1% across groups). A median difference of 27.3 hours was observed in favour of baloxavir marboxil over placebo for patients with the influenza A/H3 subtype.

Treatment-emergent amino acid changes at position 38 of the PA gene were detected in 36 out of 370 (9.7%) patients with evaluable samples in the baloxavir marboxil group compared with zero of 95 patients in the placebo group.

Study 1518T0821 in otherwise healthy adults

This was a randomised, double blind, placebo controlled Phase II study of baloxavir marboxil in otherwise healthy adult patients with influenza. It was conducted in Japan in 2015 and 2016. The primary objective was to evaluate the efficacy of baloxavir marboxil 10 mg, 20 mg, and 40 mg versus placebo assessed by the time to alleviation of symptoms in patients with uncomplicated influenza.

Eligible patients were randomised 1:1:1:1 to receive a single dose of study drug (10, 20, 40 mg or placebo on Day 1). A total of 400 adult patients were randomised and included in the intention-to-treat infected (ITTI) population. A total of 389 completed the study and 368 were included in the per protocol set (PPS). In the ITTI population, 75% to 79% were infected with influenza A (most commonly influenza A/H1N1pdm) and 21% to 25 % with the influenza B subtype.

Results of the primary efficacy endpoint

The primary efficacy endpoint is the TTAS. The study showed that the median TTAS was shorter in patients treated with baloxavir marboxil than in patients treated with placebo for all 3 baloxavir marboxil dose groups. The median difference from placebo was 23.4 hours (95% CI -35.5, -4.6) in the 10 mg baloxavir marboxil group, 26.6 hours (95% CI -38.4, -8.6) in the 20 mg group, and 28.2 hours (95% CI -39.8, -7.0] in the 40 mg group (stratified generalised Wilcoxon test: $p < 0.05$ for all comparisons).

Table 3: Study 1518T0821 results of primary endpoint; time to alleviation of symptoms

	Baloxavir marboxil			
	10 mg (N=100)	20 mg (N=100)	40 mg (N=100)	Placebo (N=100)
Primary Endpoint				
Time to alleviation of symptoms (hours)	(n=100)	(n=100)	(n=100)	(n=100)
Median [95% CI]	54.2 [47.7, 66.8]	51.0 [44.5, 62.4]	49.5 [44.5, 64.4]	77.7 [67.6, 88.7]
Median difference vs. placebo [95% CI] [a]	-23.4 [-35.5, -4.6]	-26.6 [-38.4, -8.6]	-28.2 [-39.8, -7.0]	-
P-value [b]	0.0085	0.0182	0.0046	-

a: 95% CIs for median difference was a post hoc analysis. Bootstrap estimates. b: Stratified generalized Wilcoxon test. Stratification factors: smoking habit and composite symptom score at Baseline.

There was no meaningful dose-response relationship for the primary endpoint, however, there were trends in favour of the higher baloxavir marboxil doses for the secondary endpoints. For example, each dose of baloxavir marboxil significantly reduced time to resolution compared with placebo with a modest dose-response relationship. The median time to resolution of fever was 33.4, 31.6, and 28.9 hours in the baloxavir marboxil 10 mg, 20 mg, and 40 mg groups, respectively, compared with 45.3 hours in the placebo group. The 40 mg dose was selected to take forward in the Phase III Study 1601T0831 with the additional 80 mg for subjects who weigh more than 80 mg.

Study 1601T0832 in patients who are at high risk for complications

Study 1601T0832 was a randomised, double blind, multicentre, parallel group, placebo and active controlled study. The study was to evaluate the efficacy and safety of a single dose of baloxavir marboxil for the treatment of uncomplicated influenza in patients older than 12 years of age who are at high risk of developing influenza complications. Eligible patients were randomized in a 1:1:1 ratio to receive a single oral dose of baloxavir marboxil, repeated doses of oseltamivir (75 mg BID for 5 days), or placebo. The dose of baloxavir marboxil was based on the patient's body weight. Patients were also stratified by baseline symptom score, pre-existing and worsened symptoms (yes or no), region, and body weight. The inclusion criteria for Study 1601T0832 were similar to those of Study 1601T0831 but with no upper age limit (compared with upper age limit of 64 years in Study 1601T0831) and the additional requirement for at least one high risk factor for developing influenza complications, which were exclusion criteria in Study 1601T0831. The high risk factors were based on the CDC definition of health factors known to increase the risk of developing serious complications from influenza.[6]

The primary efficacy objective was to assess the efficacy of a single dose of baloxavir marboxil compared with placebo by measuring the time to improvement of influenza symptoms in patients with influenza. The primary efficacy endpoint was the time to improvement of 7 symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), which was the time to alleviation of influenza symptoms with modification for pre-existing symptoms.

A total of 2184 patients were randomised and 2075 patients completed the study (approximately 95% in each group). A total of 109 patients did not complete the study most commonly because of withdrawal of consent; lost to follow-up; adverse events (AEs); and protocol deviations. There were 33, 34, and 42 withdrawals in the baloxavir, placebo, and oseltamivir groups, respectively.

Results of the primary efficacy endpoint

The primary efficacy analysis population (ITTI population) comprised 1163 of the randomised patients: 388 patients in the baloxavir marboxil group, 386 patients in the placebo group, and 389 patients in the oseltamivir group.

The primary efficacy endpoint was achieved in the ITTI analysis. A statistically significant improvement in the primary endpoint was observed for baloxavir marboxil when compared to placebo. The median time to improvement of symptoms (TTIS) was 73.2 hours (95% CI: 67.2, 85.1) in the baloxavir marboxil group compared with 102.3 hours (95% CI: 92.7, 113.1) in the placebo group. The median treatment difference was -29.1 hours ($p < 0.0001$). The median time to improvement of symptoms in the oseltamivir group was 81.0 hours (95% CI: 69.4, 91.5). The median difference between the baloxavir marboxil and oseltamivir groups was not significant (-7.7 hours, $p = 0.8347$).

Table 4: Study 1601T0832, intention-to-treat infected population, results of the primary endpoint; time to improvement of influenza symptoms

	Median [95% CI] (Hours)						
	Bxm (N = 388)	Placebo (N = 386)	Oseltamivir (N = 389)	Median Difference vs. Placebo (Hours) [a]	P-value [b]	Median Difference vs. Oseltamivir (Hours) [a]	P value [b]
Primary Endpoint							
Time to improvement of influenza symptoms	(n = 385) 73.2 [67.2, 85.1]	(n = 385) 102.3 [92.7, 113.1]	(n = 388) 81.0 [69.4, 91.5]	−29.1 [−42.8, −14.6]	<0.0001	−7.7 [−22.7, 7.9]	0.8347

a: 95% CIs for the median difference are provided where available. Bootstrap estimates. b: P-values based on the stratified generalized Wilcoxon test: Stratification factors: region, composite symptom scores at baseline, and pre-existing and worsened symptom. Bxm = baloxavir marboxil.

Sensitivity analyses of the primary endpoint in the ITT population and the analysis of the primary endpoint using the PPS population confirmed the results of the primary analysis. Results of secondary endpoints were generally consistent with the primary endpoint and supportive of the clinical benefit of baloxavir marboxil.

Analysis by viral subtype showed a clinically meaningful reduction in median time to improvement of influenza symptoms in the baloxavir marboxil group compared with the placebo group for both influenza A/H3 and influenza B viral subtypes and compared with oseltamivir for the B types. A median difference of -125 hours in favour of baloxavir marboxil over placebo for the influenza A/H1N1pdm subtype was also observed, although the number of patients infected with A/H1N1pdm subtype was limited in this study.

Study 1518T0822

In Study 1518T0822, open label baloxavir marboxil was given as single weight-based doses of 5 mg, 10 mg, 20 mg, or 40 mg to otherwise healthy paediatric patients aged six months to < 12 years. Only two patients aged < 2 years were enrolled. Efficacy could not be assessed as there was no active comparator or placebo group. However, the median time to alleviation of influenza illness (45 hours) was consistent with the adult studies, Studies 1601T0831 (54 hours), 1518T0821 (54 hours), and 1601T0832 (73 hours).

Clinical safety

Safety analysis from the clinical studies

The conclusion from the clinical evaluation is that no significant safety concerns were identified when baloxavir marboxil 40 mg or 80 mg was administered to patients with uncomplicated influenza. In the pooled OwH studies, baloxavir marboxil was well tolerated and the majority of symptoms were mild or moderate in severity. The most

commonly reported severe AE in the pooled analysis was bronchitis (0.8%, 1.0% and 0.2%, in the baloxavir marboxil, placebo and oseltamivir groups, respectively). There were no drug-related serious adverse events (SAEs) and no fatalities. There was a trend towards a reduced incidence of AEs in the baloxavir marboxil group compared with the placebo and oseltamivir groups. There was no evidence of drug-related hepatic impairment. Neuropsychiatric symptoms were identified as a potential risk based on oseltamivir reports; however, there was no evidence of such events in the OwH studies. The incidence of AEs was not influenced by age or gender. The incidence of AEs was higher in Japanese patients compared with White patients and this was associated with approximately 30% higher baloxavir exposure in the popPK model. In the HR study, a lower percentage of patients in the baloxavir marboxil group reported AEs compared with the placebo and oseltamivir groups. Baloxavir marboxil was well tolerated and the majority of symptoms were mild or moderate in severity. Grade 3 events were reported in 1.5%, 1.8%, and 1.7% of the respective groups and no patients in the baloxavir marboxil group reported Grade 3 or 4 AEs. The most commonly reported AEs were bronchitis, sinusitis, diarrhoea, and nausea. However, the incidence of each of these AEs was lower in the baloxavir marboxil group compared with the placebo and oseltamivir groups (see Table 5, below). There were no drug-related SAEs and no fatalities in the baloxavir marboxil group. AEs leading to drug withdrawal were reported in only four patients in the baloxavir marboxil group.

Table 5: Adverse events occurring in > 1% of patients in the baloxavir marboxil group in pooled otherwise healthy + high risk; Studies 1601T0831, 1518T0821 and 1601T0832

	Baloxavir marboxil N = 1440[a]	Placebo N = 1136	Oseltamivir N = 1234
Preferred Term	n (%)	n (%)	n (%)
Diarrhoea	40 (2.8)	40 (3.5)	34 (2.8)
Bronchitis	38 (2.6)	50 (4.4)	48 (3.9)
Nausea	28 (1.9)	34 (3.0)	50 (4.1)
Sinusitis	21 (1.5)	29 (2.6)	27 (2.2)
Headache	15 (1.0)	13 (1.1)	13 (1.1)
Alanine aminotransferase increased	15 (1.0)	12 (1.1)	9 (0.7)

[a] 40 mg and 80 mg dose groups only.

Overall, baloxavir marboxil was well tolerated and no safety signals or concerns were identified in the clinical development program.

Hypersensitivity reactions in post-marketing analysis (United State and Japan)

Based on the review of data from all completed and ongoing studies with baloxavir marboxil, no clear relationship between hypersensitivity events and baloxavir marboxil could be determined, as no AEs of anaphylaxis/anaphylactic reaction or other similar serious reactions were reported in baloxavir marboxil groups of completed or ongoing open-label clinical studies or in any treatment group of blinded ongoing studies.

An estimated cumulative total of [Information redacted] patients have received baloxavir marboxil since March 2018. At the time of the initial submission to the TGA, the evaluation of hypersensitivity reactions received from post-marketing sources was ongoing. This evaluation has now been completed, and the sponsor is proposing to update its labelling to include adverse drug reaction text about hypersensitivity reactions. The intention to make this change was originally notified to the TGA on 12 June 2019, and the revised PI was

later included with the response to TGA questions. The Drug Safety Report 1095117 is also submitted with the response to TGA questions.

Due to the typically rare frequency of drug related hypersensitivity reactions, post-marketing data are considered more likely to provide information to allow for the evaluation of these events. While large volumes of AEs may be received from the post-marketing phase, the majority of reports often lack sufficient detail for a full medical assessment and therefore these poorly documented cases are not considered to add to the weight of evidence when determining causal relationship.

Of the 29 SAEs of anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction, 16 SAEs had insufficient information for medical assessment and 4 SAEs were confounded by concomitant medication or concurrent illness. Upon review of the 9 SAEs with no or limited confounding factors, 5 were considered to meet Sampson's criteria of anaphylaxis.[7] For these events, the role of baloxavir marboxil could not be excluded. Finally, the 4 remaining SAEs were considered to be representative of a hypersensitivity or allergic response following treatment with baloxavir marboxil with patients typically experiencing swelling in the facial area or throat, skin eruption, or urticaria.

Within the categories of angioedema and urticaria, a number of events (7 and 13 events, respectively) may be causally associated with baloxavir marboxil treatment. Severe cutaneous reactions are typically drug related and were therefore reviewed as a separate category. While one clear documented event of acute generalised exanthematous pustulosis (AGEP) was reported, the remaining events assessed in this category were either considered confounded or too poorly documented for further assessment (as in the case of the two reports of Stevens–Johnson syndrome (SJS)). The remaining hypersensitivity events were not considered to be related to the use of baloxavir marboxil, as these were either too poorly documented for further assessment or were considered to be confounded by the use of concomitant medications, reported co-suspect medication, or other factors.

Based on the review of the post-marketing data (up to February 2019), the sponsor believes that baloxavir marboxil is likely to be causally associated with hypersensitivity reactions characterized by the features of urticaria, angioedema and anaphylaxis/anaphylactic reaction and recommends an update to the company core datasheet.

In view of the serious nature of these reactions, the Delegate is requesting that these reactions should be included in Section 4.4 'Special Warnings and Precautions for Use' of the PI.

The effects of treatment-emergent amino acid substitutions

The effects of treatment-emergent amino acid substitutions identified in Studies 1601T0831, 1518T0821, and 1601T0832 on drug susceptibility to baloxavir were investigated using recombinant viruses generated by reverse genetics techniques. In the absence of published criteria for indicating reduced susceptibility to baloxavir marboxil, the current World Health Organization (WHO) guidelines for neuroaminidase inhibitors were applied; thus, a 10 fold change in the half maximal effective concentration (EC_{50}) of baloxavir for the recombinant virus harboring the amino acid substitution to that of the wild type strain was used to indicate reduced susceptibility to baloxavir for type A virus and a 5 fold change was used to indicated reduced susceptibility for type B virus.[8]

[7] Sampson, H.A. et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, *Journal of Allergy and Clinical Immunology*, 2006; 117: 391-397.
[8] Gubareva, L.V. et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2015–2016, *Antiviral Res*, 2017; 146: 12–20.

In OwH Studies 1601T0831 and 1518T0821, treatment emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in recombinant influenza strains were PA/I38T (A/H3N2 (fold change 48.90 to 56.59), A/H1N1 (fold change 27.24), B (fold change 5.76)), PA/I38F (A/H1N1 (fold change 10.61)), and PA/I38M (A/H3N2 (fold change 13.77)). In HR Study 1601T0832, treatment emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in recombinant strains were PA/I38T (A/H3N2, B), PA/I38M (A/H3N2), and PA/I38N (A/H1N1 (fold change 23.66)). For all other treatment-emergent amino acid substitutions detected in these clinical studies, including all non-I38 substitutions, the fold change was < 10 for type A virus and < 5 for type B virus. Thus, overall, treatment emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in the OwH and HR studies were PA/I38T, F, M, and N. The incidence of treatment-emergent PA/I38X substitutions in patients treated with baloxavir marboxil in the three studies (Studies 1601T0831, 1601T0832, and 1518T0821) is presented in Table 6, below.

Table 6: Incidence of treatment-emergent polymerase acidic protein /I38X substitutions in patients treated with baloxavir marboxil in the three studies (Studies 1601T0831, 1601T0832, and 1518T0821)

Study	Total	Virus Type/Subtype		
		A/H1N1pdm	A/H3	B
OwH Phase 3 Study T0831	36/370 (9.7%)	0/4 (0%)	36/330 (10.9%)	1/37 (2.7%)
OwH Phase 2 Study T0821	4/182 (2.2%)	4/112 (3.6%)	0/14 (0%)	0/56 (0%)
HR Phase 3 Study T0832	15/290 (5.2%)	1/18 (5.6%)	13/141 (9.2%)	1/131 (0.8%)

Table 7: Treatment-emergent amino acid substitutions in the polymerase acidic gene associated with reduced susceptibility to baloxavir (Studies 1601T0831, 1518T0821 and 1601T0832)

Influenza Type/Subtype	A/H1N1	A/H3N2	B
Amino acid substitution	I38T/F/N	I38T/M	I38T

For type A virus, reduced susceptibility to baloxavir is defined as a ≥10-fold change (A virus) or ≥5-fold change (B virus) in the baloxavir EC_{50} of the recombinant virus harboring the amino acid substitution to that of the wild type strain (WHO).

In terms of clinical impact, in Phase III Study 1601T0831, the median TTAS in baloxavir marboxil-treated patients with a PA/I38 substitution was shorter than in the placebo group (median difference: -17.2 hours) but numerically longer than in baloxavir marboxil-treated patients without a PA/I38 substitution (median difference: 12 hours). None of the patients in the placebo group had a PA/I38 substitution. Results for the time to alleviation of individual symptoms and the time to resolution of fever were overall consistent with those of the primary endpoint (TTAS). Baloxavir marboxil-treated patients with PA/I38 substitutions tended to have comparable or numerically shorter median times to alleviation/resolution than patients treated with placebo and numerically longer median times to alleviation/resolution than patients without substitutions.

The sponsor should also provide the clinical impact analysis for the at risk population in Study 1601T0832.

The publicly available FDA assessment report mentioned the following:[9]

> *'In a pooled analysis of subjects with type A virus infection in Studies 1518T0821 and 1601T0831*, treatment emergent resistance-associated substitutions were associated with an increase in the time to alleviation of symptoms (TTAS) in baloxavir marboxil treatment arms. The medians of the TTAS for subjects with and without a treatment-emergent resistance associated substitution were 63.32 (n = 44) and 49.63 (n = 413) hours, respectively, and the difference was statistically significant (p = 0.0198, Mann-Whitney test). However, compared to placebo, the TTAS still remained shorter in subjects with resistance-associated substitutions (RAS) treated with baloxavir marboxil.
>
> *The presence of a resistance-associated substitution was associated with viral rebound and prolonged viral shedding (beyond Day 5) among baloxavir marboxil-treated subjects.'*

The above analysis showed that in patients infected with mutant viruses with RAS exhibited prolonged virus shedding, and the median time to symptom alleviation was longer in baloxavir recipients infected with these viruses than those infected with viruses not harbouring these substitutions.

The Delegate has requested the sponsor to review the PI statements under 'Viral resistance/clinical studies' section and in particular, the Delegate considers that the statement of *'Clinical impact of this reduced susceptibility is unknown'* is not accurate and should be revised.

Risk management plan

- The sponsor has submitted Core-risk management plan (RMP) version 2.0 (27 March 2019; data lock point (DLP) 11 March 2019) and Australian specific Annex (ASA) version 1.0 (8 April 2019) in support of this application. No further updates of the above documents have been supplied in the sponsor's response to TGA questions.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 8. [10]

Table 8: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–

[9] FDA, Center for Drug Evaluation and Research, Clinical Microbiology/Virology Review(S), Xofluza 20 mg and 40 mg tablets, baloxavir marboxil, Approval date 16 October 2019. Available from the FDA website.

[10] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	None	–	–	–	–
Missing information	Use in pregnant and lactating women	ü	–	ü	–

The evaluator is of the view that the routine pharmacovigilance activities to monitor the safety concern is acceptable.

The Delegate noted that the sponsor has agreed to provide the FDA with annual update on the emergence of resistance as a post-marketing commitment, and the update will include information from clinical trials, national and international databases, and published literature. The sponsor should also provide TGA with this information. This information can be provided with the periodic safety update reports (PSURs).

Risk-benefit analysis

Delegate's considerations

There are currently two classes of influenza anti-viral medications registered in Australia: M2 blockers (amantadine) and NAIs (oseltamivir, zanamivir and peramivir). The M2 blockers have become ineffective due to widespread, transmissible resistance; treatment of influenza is therefore limited to NAIs. There is a need for an easily administered antiviral drug with a new mechanism of action and good antiviral efficacy.

Baloxavir marboxil targets a different site of the influenza virus to that of the NAIs. Baloxavir marboxil inhibits the endonuclease of the viral polymerase complex of influenza A and B viruses and block the production of the primers necessary for transcription of the viral mRNA.

Based on the clinical evaluation, the Delegate is of the view that the results from the submitted studies have demonstrated the favourable benefit risk balance for the use of baloxavir marboxil, at the proposed dosage regimen, for the treatment of uncomplicated influenza infection in patients aged 12 and above who have been symptomatic for no more than 48 hours. The positive benefit risk balance is demonstrated in patients who are otherwise healthy as well as in patients who are at high risk of developing influenza complications. The Delegate is of the view that there is an advantage of a single dose of baloxavir marboxil versus oseltamivir which has to be taken twice daily for 5 days.

It is noted that there is inconsistency with regards to the results in patients infected with influenza B virus, the Delegate agrees this may due to small number of patients infected with B type virus in the Phase III study in the OwH population (Study 1601T0831). It is noted that in the Phase II study and Phase III study in the HR population, the statistically significant reduction in median time to symptom improvement or alleviation has been demonstrated against placebo in patients infected with type B virus.

It is noted that in the submitted Studies 1518T0821 and 1601T0831, patients infected with mutant viruses encoding the PA I38 substitution exhibited prolonged virus shedding,

and the median time to symptom alleviation was longer in baloxavir marboxil recipients infected with these viruses than those infected with viruses not harbouring these substitutions. The sponsor should provide the clinical impact analysis for the HR population in Study 1601T0832.

The Delegate noted that the sponsor has agreed to provide the FDA with an annual update on the emergence of resistance as a post-marketing commitment, and the update will include information from clinical trials, national and international databases, and published literature. The sponsor should also provide TGA with this information and this information can be provided with the PSURs.

The studied population in the two pivotal Phase III studies were patients with uncomplicated influenza as these patients were all outpatients who did not require hospitalisation. The FDA guideline describes the influenza in patients not requiring hospitalisation as uncomplicated influenza. The limitation of these studies is that the study population was limited to patients with uncomplicated influenza, therefore the role of baloxavir marboxil monotherapy or in combination with an NAI for treatment of hospitalized patients with influenza infection is unclear.

Following the TGA's recommendation, the sponsor has revised the initially proposed indication to the following:

> *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.*

The Delegate considers that the above revised indications acceptable and proposes the registration approval of baloxavir marboxil (Xofluza) for the revised indications.

The proposed weight-based dosing is supported by the submitted data. With regards to the proposed package presentations, the sponsor has provided the justification for the proposed packages containing 20 mg tablets. The sponsor states that the 20 mg tablets have been used in clinical studies, demonstrating clinical efficacy and safety. Consistent with the strategy to supply the US market, the initial launch in Australia will be with two package presentations: 2 x 20 mg tablets and 2 x 40 mg tablets. The 20 mg and 40 mg tablets offer maximum flexibility in terms of supply globally, and the available packs for 40 mg and 80 mg total dose reduce the possibility of over-dosing as patients receive a single pack with the dose they require. The different packs follow the Roche Family Design, with a colour assigned per tablet strength:

- 2 x 20 mg and 4 x 20 mg: orange
- 1 x 40 mg and 2 x 40 mg: blue

The sponsor has communicated their plan to develop 80 mg tablets in the future, and the package presentations will then be changed to 1 x 40 mg and 1 x 80 mg with the aim of enhancing patient convenience. The Delegate accepts the justification for the current proposed package presentations. The sponsor should monitor any reported medication errors and additional communications to the Health Care professional may be required.

The Delegate is requesting further revisions to the PI. The finalisation of this submission is subject to the satisfactory resolution of the PI and the agreement on the Conditions of Registration.

The sponsor is requested to submit the revised PI by 24 January 2020.

Proposed action

The Delegate proposes the registration approval of Xofluza for the revised indications below:

> *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*

Further revisions to the PI have been requested.

The finalisation of this submission is subject to the satisfactory resolution of the PI and the agreement on the conditions of registration.

Independent expert clinical advice

The Delegate sought and received independent expert clinical advice in the field of infectious diseases.

Advisory Committee Considerations[11]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xofluza (baloxavir marboxil) 20 mg and 40 mg film coated tablets, indicated for:

> *Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 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.*

Specific conditions of registration applying to these goods

- Provide TGA with the Annual Reports regarding the Update on the Emergence of Resistance, up to December 2023.
- Xofluza (Baloxavir marboxil) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Xofluza must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

[11] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- The Xofluza Core-RMP (version 2.0, dated 27 March 2019 DLP 11 March 2019), with ASA (version 1.0, dated 8 April 2019), included with submission PM-2019-01386-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Xofluza approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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