Taiwan Food and Drug Administration

Assessment Report

Trade Name：紓伏效膜衣錠 20 毫克
XOFLUZA Tablets 20mg

Active Ingredient：Baloxavir marboxil

License Number：MOHW-PI 027693

Applicant：台灣塩野義製藥股份有限公司

Approval Date：2019/6/24

Indication：
XOFLUZA 適用於治療成人及 12 歲以上兒童之 A 型及 B 型流行性感冒病毒急性感染。

XOFLUZA is indicated for the treatment of acute influenza infected with influenza A or B virus in patients 12 years of age and older.

1. Background Information

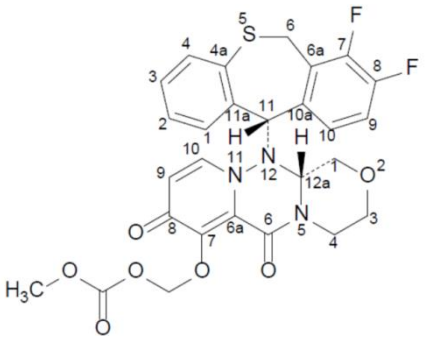
Trade Name	紓伏效膜衣錠 20 毫克 / XOFLUZA Tablets 20mg
Active Ingredient(s)	Baloxavir marboxil
Applicant	台灣塩野義製藥股份有限公司
Dosage Form & Strengths	Tablets 20mg
Indication	XOFLUZA is indicated for the treatment of acute influenza infected with influenza A or B virus in patients 12 years of age and older.
Posology	For adults and children 12years of age or older, two XOFLUZA 20mg tablets (40mg of baloxavir marboxil) should be usually administered in a single oral dose. For patients weighing 80kg or more, however, four XOFLUZA 20mg tablets (80mg of baloxavir marboxil) should be administered in a single oral dose.
Pharmacological Category **ATC Code**	J05AX25

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of baloxavir marboxil is ({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1*H*-[1,4] oxazino[3,4-*c*]pyrido[2,1-*f*][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate corresponding to the molecular formula $C_{27}H_{23}F_2N_3O_7S$. It has a relative molecular weight of 571.55 g/mol and the following structure:



Baloxavir marboxil is a white to light yellow, non-hygroscopic powder which is freely soluble in dimethyl sulfoxide, soluble in acetonitrile, slightly soluble in methanol and ethanol, and practically insoluble in water.

Baloxavir marboxil contains 2 asymmetric carbon atoms. The structure of baloxavir marboxil is confirmed by ^{1}H-NMR, ^{13}C-NMR, elemental analysis, mass spectrum, IR spectrum, UV spectrum, and X-ray crystallography.

The specification for drug substance includes suitable test items to confirm the quality.

2.1.2 Drug product

Xofluza® Tablets 20 mg is an immediate release tablet for oral administration containing 20 mg of baloxavir marboxil packaged in an aluminum blister. All compendial excipients and all individual components of coating material used in the drug product formulation comply with compendial monographs.

Adequate release and shelf-life specifications have been presented for the Xofluza® Tablets 20 mg. The release specification for drug product includes appropriate tests for film-coated tablets. Analytical methods are described and well validated.

Stability studies of drug product under long term condition (25℃/60% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Baloxavir marboxi1 (S-033188) is a prodrug that has an anti-influenza virus activity. An active form baloxavir (S-033447) produced through metabolism (hydrolysis) acts on cap-dependent endonuclease (CEN), an influenza virus-specific enzyme, and thereby inhibits the transcription of influenza virus genomes and results in inhibition of influenza virus replication.

In the *in vitro* and *in vivo* pharmacology studies, S-033188 has demonstrated the efficacy on the CEN and virus replication inhibition, improvement in survival rate, suppression of body weight loss, and inhibition of increase in body temperature. Safety pharmacology studies revealed no significant effects on the cardiovascular, CNS and respiratory system. S-033188 did not affect hERG current at any concentration tested. The IC_{50} on the hERG current was estimated to exceed 10 μM (5.72 μg/mL) for S-033188 and be 15.11 μM (7.31 μg/mL) for S-033447.

2.2.2 Toxicological Studies

Repeated-dose toxicity studies were conducted in rats and monkeys up to 4 weeks. The most important toxicological findings in the safety evaluations of S-033188 were blood chemistry

parameters suggesting disorder of hepato-biliary function such as increased levels of AST, ALT, GLDH, LAP, and GGT in plasma in the monkey without histopathological correlates. The electron microscopic analysis using liver specimens collected in monkeys disclosed that no abnormal changes were detected in the ultrastructure of hepatocytes. Given that no serious hepatic dysfunction was observed in clinical studies, baloxavir is unlikely to pose toxicological concern about its effect on the liver.

The reproductive and developmental toxicity studies revealed no significant evidence of teratogenicity of S-033188, and the increased incidence of fetal skeletal variation in rabbits was observed at a dose that caused adverse changes in dams. S-033447 and S-033188 were not genotoxic *in vitro* and *in vivo*. No significant findings of the skin phototoxicity, and juvenile toxicity were observed.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Baloxavir marboxil (S-033188) is rapidly hydrolyzed by esterase in the small intestine, blood and liver and converted to an active form baloxavir (S-033447). Plasma baloxavir marboxil concentration was below LLOQ at most time points in clinical PK studies.

Following a single oral administration of baloxavir marboxil, the Tmax of baloxavir was 4 hours in the fasted state. The absolute bioavailability of baloxavir marboxil has not been evaluated. Baloxavir exposures (C_{max} and AUC) increased in a near dose-proportional manner in the dose range from 6 to 80 mg. Food intake decreased baloxavir for C_{max} by 48% and $AUC_{0\text{-last}}$ by 36%, respectively. In clinical studies with influenza patients where baloxavir marboxil was administered with or without food, no clinically relevant differences in efficacy were observed. There was no substantial difference in PK between patients with influenza virus infection and healthy adults.

The binding of baloxavir to human serum proteins was 92.9% to 93.9%. Blood-to-plasma ratio ranged between 48.5% to 54.4%. The V_d/F of baloxavir was approximately 1180 L. The *in vitro* metabolism study revealed that baloxavir marboxil was hydrolyzed by arylacetamide deacetylase (AADAC) into baloxavir, and then metabolized by oxidation (primarily by CYP3A4) and glucuronidation (primarily by UGT1A3). In healthy adults who received a single oral dose of [^{14}C]-baloxavir marboxil 40 mg, 80.1% and 14.7% of the dosed radioactivity were excreted into the feces and the urine, respectively. In the plasma, baloxavir was detected predominantly and accounted for 82.18% of plasma radioactivity. The apparent terminal elimination half-life of baloxavir was 79.1 hours.

2.3.2 Interaction Studies

No clinically significant changes in the PK of baloxavir marboxil and baloxavir were observed when co-administered with itraconazole (strong CYP3A and P-gp inhibitor), probenecid (UGT inhibitor), or oseltamivir. No clinically significant changes in the PK of midazolam (CYP3A4 substrate), digoxin (P-gp substrate), rosuvastatin (BCRP substrate), or oseltamivir were observed when co-administered with baloxavir marboxil. Based on baloxavir marboxil's chemical structure, co-administration of baloxavir marboxil with laxatives, antacids, and supplements containing polyvalent cations may decrease its absorption.

2.3.3 Special Populations

The intrinsic factors were evaluated using population PK analysis. None of age, sex, or moderate (Child-Pugh class B) hepatic impairment was found to significantly affect the PK of baloxavir. The effects of severe hepatic impairment or renal impairment on the PK of baloxavir marboxil or its active metabolite, baloxavir, have not been evaluated.

Body weight had a significant effect on the PK of baloxavir. No clinically relevant exposure difference was observed after administering the proposed weight-based dose between subjects with lower body weight (40 mg for patients weighing less than 80 kg) and high body weight (80 mg for patients weighing 80 kg and above).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase III, randomized, double-blind, placebo- and active- controlled Study [T0831] in adult and adolescent patients ≥12 to <65 years of age with a diagnosis of influenza virus infection, had demonstrated that a single dose of baloxavir marboxil 40 or 80 mg depending on patient's weight <80 kg or ≥80 kg was superior to placebo in the time to alleviation of all 7 influenza symptoms (median hours: 53.7 vs. 80.2; difference (95% CI): -26.5 (-35.8, -17.8); p<0.0001).

Another Phase III, randomized, double-blind, placebo- and active- controlled Study [T0832] in adult and adolescent patients ≥12 years of age with a diagnosis of influenza virus infection and at high risk of influenza complications, had demonstrated that a single dose of baloxavir marboxil 40 or 80 mg depending on patient's weight <80 kg or ≥80 kg was superior to placebo in the time to improvement of influenza symptoms (median hours: 73.2 vs. 102.3; difference (95% CI): -29.1 (-42.8, -14.6); p<0.0001).

2.4.2 Safety Results

In Phase 2 and 3 trials, a total of 1747 subjects received any dose of baloxavir marboxil, including 1340 subjects in two phase 3 placebo-controlled trials who received a single dose

of baloxavir marboxil.

Serious and non-serious adverse events were reported infrequently in subjects who received baloxavir marboxil. Adverse events observed in Study T0821, Study T0822, Study T0831 and Study T0832 were mainly mild or moderate in severity and mostly recovered and recovering. All treatment-related adverse events occurred with an incidence less than 5% in any of the clinical studies. No SAE was considered to be treatment-related. No death event was observed in subject who received baloxavir marboxil in any of the clinical studies.

2.5 Bridging Study Evaluation

Japanese subjects had approximately 1.5- to 2-folded higher exposure values (C_{max}, $AUC_{0\text{-}inf}$ and C_{24}) than non-Japanese subjects, which were considered due to the lower body weight in the Japanese subjects than that in the non-Japanese subjects. In addition, the population PK analysis also revealed that race (Asian and non-Asian) is the covariates on oral drug clearance (CL/F) of baloxavir. Therefore, the PK of baloxavir marboxil is determined to be ethnically sensitive.

Baloxavir marboxil in adults and children ≥ 12 years of age showed similar effect on reducing symptomatic period in influenza infection, and shared similar safety profile between Asian and non-Asian. In summary, the efficacy results and safety profiles in Asian population were comparable to those observed in overall population. The ethnic factor of baloxavir marboxil showed no significantly clinical impact.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Two adequate and well-controlled clinical studies were provided to demonstrate the efficacy of baloxavir marboxil 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. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.

3. Post-Marketing Requirements

Routine pharmacovigilance should be conducted.