CLINICAL PHARMACOLOGY REVIEW

NDA/SDN	214410/92 210854/518, 519
Submission Dates	02/16/2022 04/29/2022 (IR response, 214410/100 and 210854/533) 06/03/2022 (IR response, 214410/106 and 210854/543)
Generic Name	Baloxavir marboxil
Brand Name	Xofluza
Dosage form and Strength	Baloxavir marboxil granules for oral suspension, 40 mg/20 mL (NDA-214410) Baloxavir marboxil tablets, 40 mg, 80 mg (NDA-210854)
Indication	Approved indications: • Treatment of acute uncomplicated influenza in otherwise healthy patients 12 years of age and older who have been symptomatic for no more than 48 hours • Treatment of acute uncomplicated influenza in patients 12 years of age and older who are at high risk of developing influenza-related complications, who have been symptomatic for no more than 48 hours • Post-exposure prophylaxis (PEP) of influenza in patients 12 years of age and older following contact with an individual who has influenza Proposed indications: • Treatment of acute uncomplicated influenza in otherwise healthy patients 5 years of age and older who have been symptomatic for no more than 48 hours • Treatment of acute uncomplicated influenza in patients 12 years of age and older who are at high risk of developing influenza-related complications, who have been symptomatic for no more than 48 hours • Post-exposure prophylaxis (PEP) of influenza in patients 5 years of age and older following contact with an individual who has influenza.
Applicant	Genentech Inc.
Clinical Pharmacology Review team	Yang Zhao, Ph.D.; Kunyi Wu, Pharm.D.
OCP Division	DIDP
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Background

Baloxavir marboxil (proprietary name: Xofluza) is an influenza virus polymerase acidic endonuclease inhibitor currently approved 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 for post-exposure prophylaxis (PEP) of influenza in patients 12 years of age and older following contact with an individual who has influenza. Baloxavir marboxil tablets (NDA-210854) was

initially approved for the treatment of influenza in patients 12 years of age and older on 10/24/2018, then received approval for the indication of PEP of influenza in the same age range on 11/23/2020. Baloxavir marboxil granules for oral suspension 40 mg/20 mL (NDA-214410-Original-1) was approved for both indications in patients ≥ 12 years on 11/23/2020. However, NDAs for treatment and PEP of influenza in patients <12 years of age for either granules for oral suspension (NDA-214410-Original-2) or tablet (NDA-210854-S-05 and S-09) received a complete response on 11/23/2020, as described below.

Clinical Pharmacology data from Study CP40563 (a Phase 3 treatment study, 1 to <12 years of age), Study 1719T0834 (a Phase 3 PEP study, >1 years to adults), and Study 1703T081G (a bioequivalence study between granules vs. tablets) were reviewed in the 2020 review cycle. In the 2020 review, the dosing regimen selection in pediatric patients is based on exposure-matching (i.e., extrapolation of efficacy from adults to pediatric patients when exposures are comparable); the 2020 clinical pharmacology review team concluded that proposed dosing (b) (4) (b) (4) is acceptable. However, due to the observed high frequency of treatment emergent baloxavir resistance in the pediatric patients 1 to < 12 years (CR letter dated 11/23/2020), baloxavir marboxil was not approved for the proposed indications in this age group.

In this re-submission, the Applicant proposes to add treatment and PEP of influenza in patients 5 to <12 years of age to the approved labeling. Modified Clinical Study Reports (CSRs) for Studies CP40653 and 1719T0834 (i.e., for patients 5 to <12 years) as well as the corresponding PK data and summaries were included in this re-submission. This review only focused on the proposed labeling because the Applicant proposed the same dosing regimen in this review cycle as the one in the 2020 review cycle; a comprehensive clinical pharmacology review for patients 1 to 12 years of age has been conducted in the 2020 review cycle; and the current clinical pharmacology review team agree with the clinical pharmacology related conclusions in the 2020 review (**DARRTS review dated 11/23/2020**). In addition, exploratory exposure-response (E-R) analyses regarding the treatment-emergent resistance were conducted based on the population PK model (deemed to be acceptable in 2020 review cycle) generated exposure matrices. No statistically significant E-R relationship was identified between baloxavir exposure and treatment-emergent resistance. Please refer to the virology review for additional exploratory analyses.

Recommendation

The Office of Clinical Pharmacology has concluded that the clinical pharmacology information in this re-submission is acceptable and supports the approval of baloxavir marboxil for the proposed indications in pediatric patients 5 to <12 years of age.

Labeling Comments/Recommendations

The labeling language is still under discussion at the time when this review is finalized.

Site Inspection

An inspection for the clinical and bioanalytical sites was requested for Studies CP40563, 1719T0834, and 1703T081G. The Office of Study Integrity and Surveillance (OSIS) concluded

that an inspection is not warranted at this time (**OSIS review dated 05/25/2022**). The OSIS conducted a Remote Record Review (RRR) for the bioanalytical site (b) (4) under NDA (b) (4) and concluded that the data from the audited study were reliable. This inspection falls within the surveillance interval.

Appendix

I. XOFLUZA dosing regimen in pediatric patients 5 to <12 years of age

a) Current approved dosing regimen for treatment and PEP of influenza in patients 12 years and older[1]

Patient Body Weight (kg)	Recommended Single Oral Dose in Patients 12 Years of Age and Older
Less than 80 kg	Two 20 mg tablets taken at the same time for a total single dose of 40 mg (blister card contains two 20 mg tablets)
At least 80 kg	Two 40 mg tablets taken at the same time for a total single dose of 80 mg (blister card contains two 40 mg tablets)

b) Proposed baloxavir dosing regimen in patients 5 years and older (Table 1)

Table 1. Proposed XOFLUZA dosing regimen in pediatrics (5 years of age and older) and approved dosing in adults and adolescents

Patient Body Weight (kg)	Recommended Single Oral Dose (Tablets)	Recommended Single Oral Dose (Suspension)
<20 kg	N/A	2 mg/kg taken as a single dose
20 kg–<80 kg	40 mg (one 40 mg tablet)	40 mg (one bottle of 40 mg/20 mL suspension)
At least 80 kg	80 mg (one 80 mg tablet)	80 mg (two bottles of 40 mg/20 mL suspension)

Reviewer's comments: No detailed review was conducted to evaluate the dosing regimen in patients 5 to < 12 years of age for the re-submission. We consider the 2020 clinical pharmacology review to be comprehensive and agree with the conclusions.

II. Plasma baloxavir PK parameters in pediatrics (5 to < 12 years of age)

The Applicant included plasma baloxavir PK parameters in pediatrics (5 to < 12 years of age) in the draft label (Table 6 in USPI as shown below).

[1] https://www.accessdata fda.gov/drugsatfda_docs/label/2020/214410s000,210854s004s010lbl.pdf

Table 6 Pharmacokinetic Parameters of Plasma Baloxavir in Pediatrics (5 to < 12 Years of Age)

(b) (4)

In the response to our information request dated 04/29/2022, the Applicant clarified that Table 6 is based on Study CP40563, (b) (4) Additionally, the Applicant provided individual PK dataset from CP40563 study pediatric patients weighing < 20 kg and ≥ 20 kg, aged 5 to <12 years, to support the estimated PK parameters in Table 6. However, the review team noticed that several subjects, (b) (6) (weighing 13.4 kg, receiving a 12 mg dose), (b) (6) (weighing 15.4 kg, receiving a 4 mg dose), and (b) (6) (weighing 22.2 kg, receiving a 34 mg dose) in the dataset, received actual doses which were different from the recommended doses in the draft label.

In the response to our information request dated 06/03/2022, the Applicant further clarified that the individual PK dataset from CP40563 study pediatric patients provided on 04/29/2022 were Bayesian estimates derived from population PK model considering the actual dose received by the pediatric patients. In addition, the Applicant provided a revised Table 6 by excluding the abovementioned subjects who did not receive the recommended dose, as below.

Table 6 Pharmacokinetic Parameters of Plasma Baloxavir in Pediatrics (5 to < 12 Years of Age) – *Revised Version*

Pharmacokinetic Parameters of Plasma Baloxavir in Pediatrics[a]	XOFLUZA dose for subjects weighing < 20 kg (n=8) 2 mg/kg	XOFLUZA dose for subjects weighing ≥ 20 kg (n=55) 40 mg
AUC_{inf} (ng.h/mL)	5830 (48.5)	4360 (48.9)
C_{max} (ng/mL)	148 (48.7)	81.1 (44.0)
T_{max} (h)[b]	3.5 (2-5.5)	4.5 (2-23.5)
C24 (ng/mL)	77.9 (49.2)	52.4 (43.2)
C72 (ng/mL)	19.3 (49.7)	18.0 (50.9)

[a] Trial 5 (CP40563) summary data, mean (%CV);

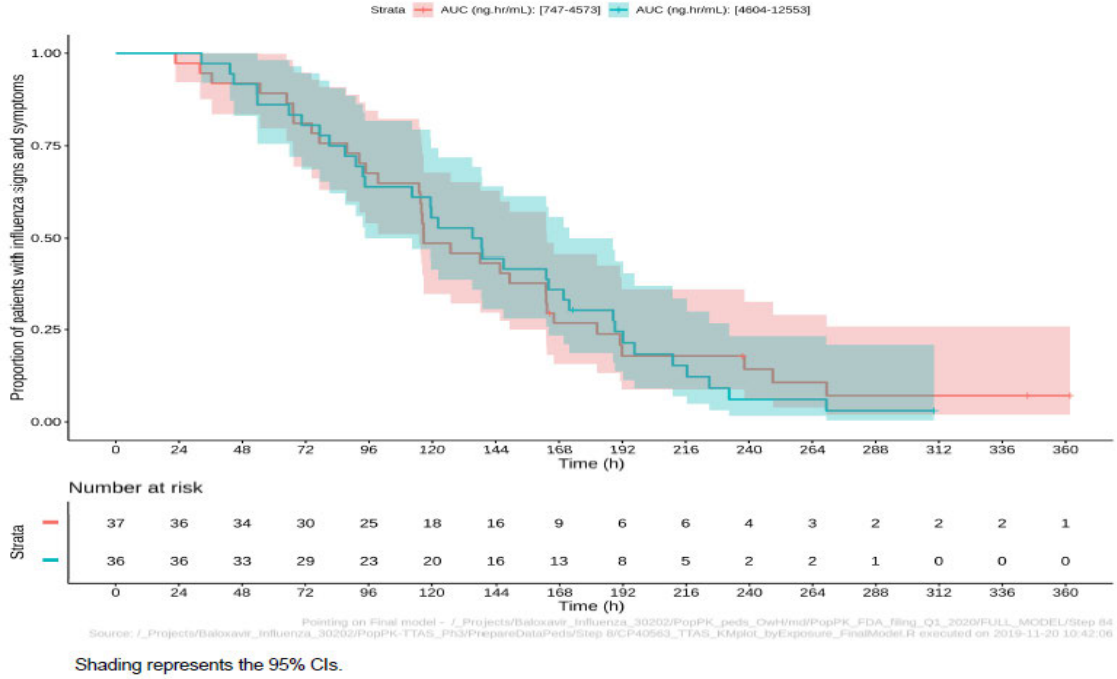
[b] Median (range)

Reviewer's comments: The clinical pharmacology reviewer's independent analyses generated similar results as the Applicant's reported values in the revised Table 6. Revised Table 6 for baloxavir PK parameters in pediatrics (5 to < 12 years of age) is acceptable.

III. Baloxavir Exposure-Response relationships in pediatrics

Baloxavir marboxil was administered 2 mg/kg for patients weighing <20 kg or 40 mg for patients weighing ≥20 kg in CP40563, (b) (4) seventy-three pediatric patients (1 to <12 years of age) treated with baloxavir marboxil in Study CP40563 were included in the exposure-efficacy analysis while seven patients were excluded from this analysis due to having PK samples below the lower limit of quantification (LLOQ). The Applicant categorized baloxavir AUC0-inf to two groups, low and high, relative to the median value of the Bayesian-estimates. The Applicant plotted the Kaplan-Meier curves of the time to alleviation of influenza signs and symptoms (TTAS, the key efficacy endpoint in CP40563 trial) per baloxavir exposure categories (low/high), together with their respective 95% confidence intervals (CI) (Figure 1). Two Kaplan-Meier curves of low and high baloxavir exposure groups overlapped, indicating that no clear exposure response is evident between baloxavir AUC0-inf and TTAS in the observed range.

Figure 1. Kaplan-Meier plot of TTAS by baloxavir exposure category, based on CP40563 study



Source: Figure 8 in Module 2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES submitted on 1/23/2020, \\CDSESUB1\evsprod\nda214410\0001\m2\27-clin-sum\summary-clin-pharm.pdf

Reviewer's comments: In the draft label, the Applicant proposed including the following statement, (b) (4)

We recommend combining the description of exposure-response relationship in adult and pediatric patients together. The recommended statement is "In patients 5 years of age and older, when XOFLUZA is dosed by weight as recommended, a flat baloxavir exposure-response (time to alleviation of influenza symptoms) relationship has been observed."

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/s/

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