Roche Genentech
A Member of the Roche Group

July 2, 2024

RESPONSE TO PREA NON-COMPLIANCE LETTER

Wendy Carter, DO
Director (Acting)
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 210854/ S-004**
NDA 214410/ Original 1
Baloxavir Marboxil (S-033188; RO7191686)
Response to PREA Non-Compliance letter

Dear Dr. Carter:

Reference is made to the following:

- Genentech Inc's Investigational New Drug Application, IND 126653 for baloxavir marboxil (S-033188; RO7191686) for the treatment of influenza, submitted to the Division of Antivirals on January 15, 2016 as Serial No. 0000.
- Genentech Inc.'s New Drug Application (NDA) 210854 approved on October 24, 2018 for the use of XOFLUZA® (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.
- Genentech Inc.'s NDA 214410/Original 1 approved on November 23, 2020 for the treatment (oral suspension, 2 mg/mL) and post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older.
- Genentech Inc.'s NDA 210854/S-04 approved on November 23, 2020 to expand the indication for XOFLUZA (baloxavir marboxil) tablets to include post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older.
- Genentech Inc.'s NDA 210854/S-09 approved on August 11, 2022 for the use of Xofluza (baloxavir marboxil) tablets for post-exposure prophylaxis of influenza in pediatric patients ≥ 5 to less than 12 years of age.

- Amendment Version 6 protocol of Study CP40559 entitled, “A Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients from Birth to < 1 Year with Influenza-Like Symptoms”, submitted on May 4, 2022 (Serial No. 0261).

- The Sponsor’s deferral extension request for PMR 3961-1 submitted to the FDA on August 30, 2023 and the deferral extension granted letter received via email on October 13, 2023 (Reference ID: 5258291).

- The Sponsor’s Clinical Study Report of Study CP40559 submitted to the FDA on December 20, 2023 as a submission of the required Pediatric Assessment

- The Notification of Non-Compliance with PREA letter received on May 22, 2024 (Reference ID: 5385394)

- Email Correspondence: Information Request/ Advice received from the FDA on May 22, 2024 with Additional Comments on the Non-Compliance letter (Reference ID: 5385476)

PMR 3961-1 as per Approval letter for NDA 210854/S-004 and NDA 214410/ original 1 received on November 23, 2020:
Submit the clinical study reports including the pharmacokinetic/pharmacodynamic modeling data and the supporting PK, safety and efficacy data from all the relevant studies in adult and pediatric patients to extrapolate efficacy of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age for the prevention of influenza as postexposure prophylaxis in household contacts of an index case. Include characterization of baloxavir-resistant substitutions including supporting datasets.

Current timelines are shown below.
Trial Completion: 08/2023
Final Report Submission: 02/2024

In response to PMR 3961-1, the Sponsor submitted the following:

- Updated PopPK modeling Report (RDR1129175): the population PK analysis is based on data from 8 completed clinical studies (CP40559, CP40563, T0822, T0833, T0835, T0821, T0831, and T0832), and the dataset included a total of 6666 plasma concentrations collected from 1884 patients, including 57 patients <1 year of age.
- Supporting document describing the methodology for the extrapolation strategy for prevention of influenza as post exposure prophylaxis in household contacts under 1 year of age
- Supporting datasets from Study CP40559 including baloxavir-resistant substitutions

These reports and supporting documents and datasets were submitted prior to the milestone deadline on February 27, 2024 as a required pediatric assessment. However, no label update was proposed with the submission, as the currently approved indication in the US is for patients 5 years and older, thus the Sponsor determined that the results from Study CP40559 did not warrant a label change for patients under 12 months of age.

The data from Study CP40559 did not adversely impact the safety or the resistance profile of the drug, and the overall benefit-risk was unaltered.

A cross-reference letter has been submitted to IND 126653.

In the Non-Compliance letter, the Agency acknowledged the submissions of the final study reports and requested the Sponsor provide draft labeling as a prior approval supplement (PAS) to NDAs 214410 and 210854, incorporating changes since the last approval of the Prescribing Information and FDA-approved patient labeling.

Accordingly, the Sponsor will submit the requested PAS to NDA 214410 and NDA 210854, incorporating the below proposed updates as recommended by FDA, on July 2, 2024.

1. Section 8.4, Pediatric Use, Pediatric Subjects (< 5 years of age).
   See proposed edits shown in red below:

   The safety and effectiveness of XOFLUZA for treatment and post-exposure prophylaxis of influenza in pediatric subjects less than 5 years of age, including neonates, have not been established.

2. Section 12.4, Microbiology, Resistance, Clinical studies in pediatric subjects < 5 years of age.

   This section has been updated to include the treatment-emergent resistance frequencies for subjects <5 years of age by including all subjects evaluated for treatment-emergent resistance in trial CP40559.

Additionally, the Sponsor has also updated Section 5.2 Increased Incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age to include all subjects evaluated for treatment-emergent resistance in trial CP40559.

This submission is being submitted electronically via the FDA ESG. CrowdStrike and/or Sentinel One (with the most recent Virus Definition File version) was used to ensure the files are virus-free. For any technical issues regarding the electronic transmission of this

submission, please contact Peter Goodwin, Regulatory Data & Content Leader, F. Hoffmann-La Roche/Genentech, Inc. at (415) 694-8999 or goodwin.peter@gene.com.

If you have any questions or need additional information regarding this submission, please contact the undersigned.

Sincerely,

Shweta Kotwal, MBBS, MA.
Regulatory Program Management
Genentech, Inc.
1 DNA Way MS# 407B
South San Francisco, CA 94080-4990
Phone: (650) 243-8340
Email: kotwal.shweta@gene.com

CONFIDENTIALITY STATEMENT

This submission contains information that constitutes trade secrets and/or is confidential within the meaning of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §331 [j]), the Freedom of Information Act (5 U.S.C. §552[b][4] and 18 U.S.C. Section 1905) and 21 CFR Sections 312.130, 314.430, 601.50, and 601.51 and may not be revealed or disclosed without the prior written authorization of Hoffmann-La Roche, Inc./Genentech, Inc.