NDA 214410/Original 2

NDA APPROVAL

Genentech, Incorporated
Attention: Shweta Kotwal, MBBS, MA
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Kotwal:

Please refer to your new drug application (NDA) dated and received January 23, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xofluza (baloxavir marboxil), 2% granules, for oral suspension.

We acknowledge receipt of your amendment dated February 16, 2022, which constituted a complete response to our November 23, 2020, action letter.

NDA 214410 provides for the use of Xofluza (baloxavir marboxil), 2% granules, for oral suspension, for the following indications which, for administrative purposes, we have designated as follows:

- NDA 214410/Original 1 – for the treatment and post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older
- NDA 214410/Original 2 – for the treatment and post-exposure prophylaxis of influenza in pediatric patients ≥ 5 to less than 12 years of age

The subject of this action letter is NDA 214410/Original 2. A separate letter for NDA 214410/Original 1 was issued on November 23, 2020.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for ages 1 to 12 years of age for the treatment and post-exposure prophylaxis of influenza indications.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated February 16, 2022, containing the final reports for the following postmarketing requirements listed in the November 23, 2020, approval letters.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Established under NDA 214410/Original 1

3984-2 Conduct a randomized active-controlled clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from 12 months to less than 12 years of age with acute uncomplicated influenza. Include characterization of baloxavir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

Established under NDA 214410/Original 1 and NDA 210854/S-4

3961-2 Submit the clinical study report including the datasets and pharmacokinetic/pharmacodynamic modeling data for the Phase 3 Study 1719T0834 conducted in pediatric subjects from 12 months to less than 12 years of age to evaluate the pharmacokinetics, safety, and efficacy of baloxavir marboxil for the prevention of influenza as post-exposure prophylaxis in household contacts of an index case. Include characterization of baloxavir resistance-associated substitutions including supporting datasets.

3961-4 Submit the full clinical study report and datasets for Study T0835 conducted to evaluate the pharmacokinetics, safety, and effectiveness of baloxavir marboxil for the treatment of acute, uncomplicated influenza in Japanese pediatric subjects < 12 years of age and < 20 kilograms in weight. The study report should include characterization of the emergence of baloxavir resistant viral variants, including supportive datasets.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the November 23, 2020, approval letters that are still open.

POSTMARKETING REQUIREMENT UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of the emergence of baloxavir-resistant influenza virus.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4316-1 Evaluate PA substitution F314S, alone and in combination with A231V, for its impact on baloxavir susceptibility in A/H1N1 virus.

The timetable you submitted on July 27, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	07/2023
Final Report Submission:	09/2023

Submit clinical protocol(s) to your IND 126653 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4316-2 Conduct a prospective, multicenter, observational study in baloxavir marboxil-treated patients over at least five influenza seasons that will capture the susceptibility and genotype of influenza viruses in baseline and on-treatment respiratory samples to determine the frequency of baseline and treatment-emergent baloxavir resistance and the impact on outcomes.

The timetable you submitted on July 27, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2023
Study Completion:	04/2027
Final Report Submission:	10/2027

4316-3 Provide a semi-annual (twice-yearly) update on global baloxavir usage and emergence of resistance to baloxavir as an integrated review of information from national and international influenza drug resistance databases and sequence databases, including but not limited to World Health Organization and US Centers for Disease Control and Prevention surveillance, data collected by the sponsor, and information in the published literature. Each update will include information on the methodologies (e.g., viral gene sequencing and phenotypic assay descriptions) used in studies during that reporting period. Substitutions of particular interest include all those listed as resistance associated in the USPI, as well as substitutions currently identified or identified in the future that reduce susceptibility to baloxavir marboxil.

The timetable you submitted on July 27, 2022, states that you will conduct this study according to the following schedule:

Interim Report Submission:	05/2023
Interim Report Submission:	11/2023
Interim Report Submission:	05/2024
Interim Report Submission:	11/2024
Interim Report Submission:	05/2025
Interim Report Submission:	11/2025
Final Report Submission:	05/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 126653 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager, at the main line at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antivirals
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBRA B BIRNKRANT
08/11/2022 01:06:59 PM