CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214410Orig1s000
210854Orig1s004,s010

Trade Name:	XOFLUZA for oral suspension
Generic or Proper Name:	baloxavir marboxil
Sponsor:	Genentech, Incorporated
Approval Date:	November 23, 2020
Indication:	The use of XOFLUZA (baloxavir marboxil), for oral suspension, for the treatment and post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older To update CLINICAL PHARMACOLOGY, Microbiology, Resistance subsection of the labeling with data from 3 treatment trials in pediatric patients 12 months to less than 12 years of age
	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
	To update CLINICAL PHARMACOLOGY, Microbiology, Resistance subsection with data from 3 treatment trials in pediatric patients 12 months to less than 12 years of age

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214410Orig1s000
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APPLICATION NUMBER:

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APPROVAL LETTER

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NDA APPROVAL
SUPPLEMENT APPROVAL-
FULFILLMENT OF POSTMARKETING
COMMITMENT

Genentech, Incorporated
Attention: Sabina Zimmerman, PhD
US Regulatory Lead
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Zimmerman:

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) for oral suspension.

We also refer to your supplemental new drug applications (sNDAs) dated and received January 23, 2020, and your amendments, submitted under section 505(b) of the FDCA for XOFLUZA (baloxavir marboxil) 20 mg and 40 mg tablets.

The aforementioned applications provide for the following:

NDA 214410/Original 1	The use of XOFLUZA (baloxavir marboxil), for oral suspension, for the treatment and post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older To update CLINICAL PHARMACOLOGY, Microbiology, Resistance subsection of the labeling with data from 3 treatment trials in pediatric patients 12 months to less than 12 years of age
NDA 210854/S-04	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
NDA 210854/S-10	To update CLINICAL PHARMACOLOGY, Microbiology, Resistance subsection with data from 3 treatment trials in pediatric patients 12 months to less than 12 years of age

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and submitted on October 21, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214410**." Approval of this submission by FDA is not required before the labeling is used.

[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.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Xofluza (baloxavir marboxil) for oral suspension shall be 30 months from the date of manufacture when stored at 20 °C to 25 °C (68 °F to 77 °F).

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.

NDA 214410/Original 1 – Treament of Influenza

We are deferring submission of your pediatric study from birth to less than 12 years of age for the treatment of influenza indication for this application because this product is ready for approval for use in adults, and additional analyses of safety or effectiveness data from the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies as listed in the October 24, 2018, approval letter for NDA 210854 are listed below:

3503-1 Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.

Final Protocol Submission:	Submitted
Study Completion:	09/2021
Final Report Submission:	12/2021

3503-2 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.

Final Protocol Submission:	Submitted
Study Completion:	09/2021
Final Report Submission:	12/2021

NDA 214410 and NDA 210854/S-04 – Post-exposure Prophylaxis

We are deferring submission of your pediatric study from birth to less than 12 years of age for the post-exposure prophylaxis indication for these applications because this product is ready for approval for use in adults, and additional analyses of safety or effectiveness data needs to be submitted for pediatric patients ages birth to less than 12 years of age.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing study(ies). The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

3961-1 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 post-exposure prophylaxis in household contacts of an index case. Include characterization of baloxavir-resistant substitutions including supporting datasets.

Final Protocol Submission:	Submitted
Study Completion:	09/2021
Final Report Submission:	12/2021

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.

Final Protocol Submission:	Submitted
Study Completion:	Completed
Final Report Submission:	12/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 126653, with a cross-reference letter to these NDAs Reports of these required pediatric postmarketing studyies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this/these study(ies). When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

This product is appropriately labeled for use in ages 12 to 17 years for the treatment of influenza indication. Therefore, no additional studies are needed in this pediatric group.

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for the influenza post-exposure prophylaxis indication.

POSTMARKETING REQUIREMENTS 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.

Since XOFLUZA was approved on October 24, 2018, we have become aware of additional treatment-emergent substitutions in influenza virus identified in clinical trials

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

that may be associated with resistance to baloxavir. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 resistant 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:

3961-3 Evaluate the impact of the following substitutions on the susceptibility of influenza virus to baloxavir in cell culture: PA substitutions R269I, V330I, K328E and T363I in A/H1N1 virus and I554V in A/H3N2 virus.

The timetable you submitted on August 28, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2020
Study Completion:	10/2021
Final Report Submission:	12/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of emergence of baloxavir resistant viral variants in pediatric patients <12 years of age.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

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.

The timetable you submitted on November 11, 2020, states that you will conduct this trial according to the following schedule:

Study Completion:	Completed
Final Report Submission:	12/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

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**

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

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated January 23, 2020, containing the final report for the following postmarketing commitment listed in the October 24, 2018, approval letter.

3503-9 Submit the clinical study report and datasets for the bioequivalence study comparing the 20 mg tablet and 2% granule formulations for baloxavir marboxil in healthy adult volunteers.

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the October 24, 2018, approval letter that are still open.

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.*[6]
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.[7]
Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

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

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

If you have any questions, call Christine Kim, PharmD, Regulatory Project Manager, at (301) 796-5964 or at the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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/

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