

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210854Orig1s000

Trade Name: Xofluza Film-Coated Tablets, 20 mg and 40 mg

*Generic or
Established:* Baloxavir marboxil

Sponsor: Shionogi, Inc.

Approval Date: October 24, 2018

Indication: Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 210854

NDA APPROVAL

Shionogi, Incorporated
Attention: Ann Howell, Pharm.D., MS
Senior Director, US Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Dr. Howell:

Please refer to your New Drug Application (NDA) dated and received April 24, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XOFLUZA™ (baloxavir marboxil) film-coated tablets, 20-mg and 40-mg.

This new drug application provides for the use of XOFLUZA™ (baloxavir marboxil) tablets 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.

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 text.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

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 container labeling submitted on September 18, 2018, and the carton labeling submitted on September 27,

2018, 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 titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4). For administrative purposes, designate this submission “Final Printed Carton and Container Labeling for approved NDA 210854.” Approval of this submission by FDA is not required before the labeling is used.

MATERIAL THREAT MEDICAL COUNTERMEASURE (MCM) PRIORITY REVIEW VOUCHER (PRV)

We refer to your request for a material threat MCM PRV for XOFLUZA for the treatment of acute, uncomplicated influenza and to the preliminary, nonbinding opinion provided in our filing communication dated June 20, 2018.

Your request for a material threat MCM PRV is denied. This application is not eligible to receive a material threat MCM PRV because, at the time of approval, it is not an application for a human drug:

- intended for use to prevent or treat harm from a CBRN agent (or harm caused by an MCM used against such agent) identified as a material threat under section 319F-2(e)(2)(A)(ii) of the Public Health Service Act, or
- intended to mitigate, prevent or treat harm from a condition that may result in adverse health consequences or death and may be caused by administering a drug or biological product against such agent.

At this time, no form of influenza is listed as a material threat that may qualify an MCM application for a PRV under section 565A(a)(4)(i) of the FDCA. See the *2017-18 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan* and section 565A(a)(4) of the FDCA.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Victoria Tyson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6392
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for XOFLUZA™ was not referred to an FDA advisory committee because the clinical trial design was acceptable, the application did not raise significant safety or efficacy issues and outside expertise was not necessary; there were no controversial issues that would have benefited from advisory committee discussion.

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 are deferring submission of your pediatric studies for ages birth to less than 12 years for this application because this product is ready for approval for use in adolescents and adults and 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)(3)(C) of the FDCA. These required studies 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/Trial 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/Trial Completion: 09/2021
Final Report Submission: 12/2021

3503-3 Submit the clinical study report and datasets for the pharmacokinetics, safety, and efficacy trial of baloxavir marboxil in Japanese pediatric subjects who weigh less than 20 kg with acute, uncomplicated influenza. Include characterization of resistance-associated substitutions, including supportive datasets.

Final Protocol Submission: submitted
Study/Trial Completion: 02/2018 (completed)
Final Report Submission: 12/2021

Reports of these required pediatric postmarketing studies 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 these studies. 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 this indication. Therefore, no additional studies are needed in this pediatric group.

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.

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 a signal of serious risk of the emergence of resistant virus.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

3503-4 Evaluate the impact of the following substitutions on susceptibility of cloned virus in cell culture to baloxavir: A/H1N1 PA: E23R, A37S, I38L, E199D, E199K, P267S, A476S, and E677D; A/H3N2 PA: F35L, V62I, T162I, E199D, E199K, Y321H, V432I, K492R, M595I, A618S, and G684R; type B PA: A37Q, I38V, G199R, K298R, T304A, V645A, and M682L; and A/H3N2 PB2: R209K.

The timetable you submitted on October 11, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2019
Study Completion: 07/2021
Final Report Submission: 12/2021

Finally, we have determined that only data collected as part of clinical trials (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of transmission of influenza virus variants with reduced susceptibility to baloxavir.

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

3503-5 Evaluate the incidence of transmission of virus carrying substitutions identified as associated with reduced susceptibility to baloxavir or otherwise potentially resistance-associated, including substitutions listed as resistance-associated in Section 12.4 of the USPI, in studies of subjects treated prophylactically with baloxavir marboxil, and from studies of influenza virus transmission.

The timetable you submitted on October 16, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 11/2018
Final Protocol Submission: 02/2019
Trial Completion: 12/2020
Final Report Submission: 06/2021

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:

3503-6 Conduct a randomized, double-blind, controlled clinical trial evaluating efficacy and safety of baloxavir marboxil in subjects hospitalized with severe influenza.

The timetable you submitted on October 16, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: submitted
Study/Trial Completion: 05/2022
Final Report Submission: 11/2022

3503-7 Submit the clinical study report and datasets for the completed Phase 3 clinical trial which evaluated efficacy of baloxavir marboxil for treatment of acute, uncomplicated influenza in patients at high risk for influenza complications 12 years of age and older.

The timetable you submitted on October 16, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: submitted
Study/Trial Completion: 04/2018 (completed)
Final Report Submission: 02/2019

3503-8 Conduct a randomized, double-blind, placebo-controlled trial of baloxavir marboxil post-exposure prophylaxis to prevent influenza in household contacts of an index case.

The timetable you submitted on October 11, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2018
Study/Trial Completion: 04/2019
Final Report Submission: 10/2019

3503-9 Submit the clinical study report and datasets for the bioequivalence study comparing the 20 mg tablet and (b) (4) formulations of baloxavir marboxil in healthy adult volunteers.

The timetable you submitted on October 11, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	submitted
Study/Trial Completion:	12/2017 (completed)
Final Report Submission:	12/2021

3503-10 Provide an annual update on emergence of resistance to baloxavir as an integrated review of information from various sources such as national and international influenza drug resistance databases and sequence databases, data collected by the Applicant, and published literature. Substitutions of particular interest include all those listed as resistance-associated in the USPI, as well as identified substitutions that reduce susceptibility to baloxavir \geq 3-fold in cell culture.

The timetable you submitted on October 16, 2018, states that you will submit annual updates according to the following schedule:

Initial Submission:	12/2019
Final Submission:	12/2023

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 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

John Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
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/

JOHN J FARLEY
10/24/2018