CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214410Orig1s000
210854Orig1s004,s010

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 27, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 210854/S-04 (b) (4) and NDA 214410
Product Name and Strength:	Xofluza (baloxavir marboxil) Tablets; 20 mg and 40 mg Xofluza (baloxavir marboxil) for oral suspension; 40 mg/20 mL (2 mg/mL)
Applicant/Sponsor Name:	Genentech, Inc. (Genentech)
OSE RCM #:	2020-162-1 and 2020-155-1
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised U.S. Prescribing Information, container label, and carton labeling received on October 22, 2020 for Xofluza. The Division of Antivirals (DAV) requested that we review the revised label and labeling for Xofluza (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a,b]

2 CONCLUSION

The Applicant implemented all of our recommendations and clarified that the expiration date format "MMYYYY" is will use numerical characters only. We have no additional recommendations at this time.

[a] Vaughan, V. Label and Labeling Review for Xofluza (NDA 210854/S-04 (b) (4) and NDA 214410). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 05. RCM No.: 2020-162 and 2020-155.
[b] Kim, C. FDA Communication: Labeling Comments for Xofluza. Silver Spring (MD): FDA, CDER, DAV (US); 2020 OCT 19. NDA 210854/S-04, (b) (4) and NDA 214410.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 22, 2020

U.S. Prescribing Information (Image not shown)

- Revised U.S. Prescribing Information received on October 22, 2020, available at: \\CDSESUB1\evsprod\nda214410\0048\m1\us\redlined-label-text.doc
- Revised Patient Package Insert received on October 22, 2020, available at: \\CDSESUB1\evsprod\nda214410\0048\m1\us\ppi-redlined.docx

Container labels

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

SEVAN H KOLEJIAN on behalf of VALERIE S VAUGHAN
10/27/2020 09:53:19 AM

SEVAN H KOLEJIAN
10/27/2020 09:53:47 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 5, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 210854/S-04 (b) (4) and NDA 214410
Product Name, Dosage Form, and Strength:	Xofluza (baloxavir marboxil) Tablets; 20 mg and 40 mg Xofluza (baloxavir marboxil) for oral suspension; 40 mg/20 mL (2 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc. (Genentech)
FDA Received Date:	January 23, 2020
OSE RCM #:	2020-162 and 2020-155
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Genentech submitted New Drug Application (NDA) 214410 for Xofluza (baloxavir marboxil) for oral suspension, 40 mg/20 mL and efficacy supplements for NDA 210854/S-4 (b) (4) to:

- add a new for oral suspension formulation for Xofluza to the Xofluza product line;
- extend the indication of Xofluza to include otherwise healthy patients 1 year of age and older who have been symptomatic for no more than 48 hours; and
- seek an indication for post-exposure prophylaxis of influenza in patients 1 year of age and older.

Subsequently, the Division of Antivirals requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Response to Information Requests	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSSESSMENT

Our evaluation of the Xofluza prescribing information (PI), packaging, container label, and carton labeling is included in Sections 3.1, 3.2, and 3.3, respectively.

3.1 PRESCRIBING INFORMATION

Xofluza (baloxavir marboxil) tablets and for oral suspension will share one PI. According to the proposed prescribing information (PI), Xofluza for oral suspension is intended for use in children aged 1 to less than 12 years of age and patients who have difficulty or are unable to swallow tablets, or who require enteral administration. Our evaluation of the Xofluza PI received on January 23, 2020 identified areas for improvement at the initial phase of the review cycle.

We note that Table 2 of the Dosage and Administration section includes two units of measurement (i.e., mg and mL), which could lead to overdose and underdose errors. Specifically, we are concerned that healthcare providers could inadvertently misinterpret the dose as "1 mg/kg" or "2 mL/kg" or "20 mg" or "40 mL" due to the presence of two units of measurement in Table 2. Prescribing oral solutions/suspensions in metric units by weight (e.g. mg/kg) is recommended by the Joint Commission to enable an independent double-check of dose calculation by a pharmacist, nurse, or both on inpatient medication orders and outpatient prescriptions.[a] In addition, dosing based on volume has resulted in medication errors for other drugs.[b] Therefore, we recommend the "(b) (4) be removed from Table 2.

Additionally, we note that Xofluza for oral suspension, once constituted, is intended to be dispensed to patients and caregivers in the glass bottle in which the drug product is supplied. (b) (4) Following constitution, each bottle contains 40 mg/20 mL of Xofluza suspension. (b) (4) Moreover, no instruction is included to clarify that more than one bottle may be needed when the intended dose is 80 mg, for example, in adults or adolescents at least 12 years of age and weighing at least 80 kg who have difficulty or are unable to swallow tablets.

(b) (4)

[a] The Joint Commission. Preventing pediatric medication errors. Sentinel Event Alert. 2008;39. Available from: https://www.jointcommission.org/-/media/deprecated-unorganized/imported-assets/tjc/system-folders/topics-library/sea_39pdf.pdf?db=web&hash=29D89AF0947F063B82967B81E640CBBC

[b] Institute for Safe Medication Practices. 2016 May. Prescribing and dispensing errors with oral solutions. ISMP Med Saf Alert Community/Ambulatory Care. 15(5):1-3.

(b) (4) Therefore, OPQ requested a repeat microbiology challenge study.

On September 30, 2020, in response to the Agency's August 10, 2020 information request[c], Genentech submitted new data from a repeat microbiology challenge study for Agency review. (b) (4) y. Therefore, the Genentech opted to complete the challenge study utilizing bottled drinking water. Based on the new data, our Product Quality Microbiology colleagues determined that a post-constitution hold time of 10 hours at 20-25°C when Xofluza for oral suspension is prepared with drinking water (e.g., tap water, filtered tap water, or bottled water) or sterile water is supported by the study results. A hold time of 10 hours addresses our concern for administration errors. To minimize the risk for preparation or administration errors, we recommend revisions to align the preparation instructions across the PI and carton labeling for Xofluza for oral suspension.

In collaboration with the review team we proposed revisions to the Dosage and Administration, Dosage Forms and Strengths, and How Supplied/Storage and Handling sections of the PI to minimize risk of overdose/underdose, preparation, administration, and storage errors, which were previously communicated to the applicant.[d,e,f]

3.2 PACKAGING

The proposed Xofluza for oral suspension formulation will be supplied as a single strength, 40 mg per bottle, to cover the therapeutic dosages 2 mg/kg, 40 mg, and 80 mg based on patient age and weight (See *Dose and Frequency*, Appendix A). The entire bottle is intended to be dispensed to patients/caregivers to administer a one-time dose. (b) (4) Additionally, we are concerned for risk of underdose errors when the intended dose is 80 mg, which requires dispensing 2 bottles. We discussed our concern for overdose (b) (4) errors with the clinical review team. The clinical team stated that no concerning adverse events were reported with overdose errors in

[c] Kim, C. FDA Communication: Information request for Xofluza. Silver Spring (MD): FDA, CDER, DAV(US); 2020 AUG 10. NDA 214410, NDA 210854/S-04, (b) (4)
[d] Kim, C. FDA Communication: Labeling Comments for Xofluza. Silver Spring (MD): FDA, CDER, DAV (US); 2020 JUL 16. NDA 214410, NDA 210854/S-04, (b) (4)
[e] Kim, C. FDA Communication: Labeling Comments for Xofluza. Silver Spring (MD): FDA, CDER, DAV (US); 2020 AUG 14. NDA 214410, NDA 210854/S-04, (b) (4)
[f] Kim, C. FDA Communication: Labeling Comments for Xofluza. Silver Spring (MD): FDA, CDER, DAV(US); 2020 AUG 28. NDA 214410, NDA 210854/S-04, (b) (4)

clinical trials or postmarketing reports received for Xofluza. Additionally, per the clinical team, the safety data from the highest exposures with few adverse events (AEs) and no severe or serious AEs are reassuring. (b) (4) Thus, we collaborated with the review team to revise the PI in order to minimize the risk of (b) (4) overdose errors. Additionally, Genentech revised the container label and carton labeling to clarify to "take volume prescribed" for patients/caregivers (see Appendix G).

3.3 CONTAINER LABELS AND CARTON LABELING

We reviewed the container label and carton labeling for the new proposed Xofluza for Oral Suspension formulation received on January 23, 2020. Our evaluation of the container label and carton labeling identified areas for improvements at the initial phase of the review cycle. Thus, we proposed the following recommendations to Genentech to minimize preparation and storage errors[9]:

1. Include the constitution instructions on the side panel of the carton labeling. Ensure the instructions align with the instructions included in the Dosage and Administration section of the Prescribing Information. Additionally, because the instructions will be included on the side panel, remove the statement, "See Prescribing Information (b) (4) ."
2. Clarify the format you intend to use to indicate the expiration date.
3. Revise the storage recommendations for constituted Xofluza to align with the storage recommendations indicated in the Prescribing Information.

On July 30, 2020, Genentech submitted revised container labels and carton labeling that included implementation of our recommendations #1 and 3 above (see Appendix G). Regarding recommendation #2, Genentech indicated they will use the format "MM YYYY" to express the expiration date. We note that Genentech did not specify if the month (i.e., MM) will be displayed using numerical (e.g., 06) or alphabetical (e.g., JU) characters. Thus, we provide recommendation in Table 2 to ensure numerical characters are utilized to denote the month of the expiration date to minimize risk of confusion.

Additionally, based on results of a new microbiology challenge study, the preparation, administration time, and storage recommendations have been revised in the USPI, thus, to minimize risk of medication error, we provide recommendation to align this information across all Xofluza label and labeling.

4 FINDINGS AND RECOMMENDATIONS

Table 2 below include the identified medication error issues with the submitted container label and carton labeling, DMEPA's rationale for concern, the proposed recommendation to minimize

[9] Kim, C. FDA Communication: Carton/Container Labeling Comments for Xofluza. Silver Spring (MD): FDA, CDER, DAV(US); 2020 JUL 20. NDA 214410.

the risk for medication error, and a general comment regarding the final presentation of the container labels and carton labeling for Xofluza for Oral Suspension.

Table 2: Identified Issues and Recommendations for Genentech (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling (Xofluza for oral suspension)			
1.	The proposed expiration date (i.e., MM YYYY) does not specify whether the month (i.e., MM) will be displayed using numerical (e.g., 06) or alphabetical (e.g., JU) characters.	Use of two-digit alphabetical characters (e.g., JU) could lead to confusion or misinterpretation and increases the risk for deteriorated drug medication errors.	For the proposed expiration date format (i.e., MM YYYY), ensure the month is denoted by numerical characters (e.g., 06).
2.	The preparation, administration times, and storage included on the container label and carton labeling do not align with the USPI.	Discrepancies could lead to preparation, administration, or storage errors.	Revise the diluents used for constitution of Xofluza for oral suspension, administration time following constitution, and the storage following constitution described on the container label and carton labeling to align with the USPI.

5 CONCLUSION

Our evaluation of the proposed prescribing information, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Xofluza received on January 23, 2020 and September 4, 2020 from Genentech, Inc.

<table>
<tr><th colspan="2">Table 1. Relevant Product Information for Xofluza</th></tr>
<tr><td>Initial Approval Date</td><td>Tablets: 10/24/2018
For Oral Suspension: N/A</td></tr>
<tr><td>Active Ingredient</td><td>baloxavir marboxil</td></tr>
<tr><td>Indication</td><td>1.1 Treatment of Influenza

XOFLUZA is indicated for the treatment of acute uncomplicated influenza in otherwise healthy patients 1 year of age and older and in patients 12 years of age and older who are at high risk of developing influenza-related complications,1 who have been symptomatic for no more than 48 hours

1.2 Post-Exposure Prophylaxis of Influenza

XOFLUZA is indicated for post-exposure prophylaxis of influenza in persons 1 year of age and older following contact with an individual who has influenza</td></tr>
<tr><td>Route of Administration</td><td>Oral; Enteral</td></tr>
<tr><td>Dosage Form</td><td>Tablets; For Oral Suspension</td></tr>
<tr><td>Strength</td><td>Tablets: 20 mg and 40 mg
For Oral Suspension: 40 mg per bottle</td></tr>
<tr><td>Dose and Frequency</td><td>Recommended XOFLUZA Tablet Dosage in Adults and Adolescents (12 Years of Age and Older)
<table>
<tr><th>Patient Body Weight (kg)</th><th>Recommended Single Oral Dose (Tablets)</th></tr>
<tr><td>(b) (4) less than 80 kg</td><td>Two 20 mg tablets taken at the same time for a total single dose of 40 mg
(blister card contains two 20 mg tablets)</td></tr>
<tr><td>At least 80 kg</td><td>Two 40 mg tablets taken at the same time for a total single dose of 80 mg
(blister card contains two 40 mg tablets)</td></tr>
</table></td></tr>
</table>

	For adults and adolescents 12 years of age and older who are unable to or have difficulty swallowing tablets, XOFLUZA for oral suspension may be used at the same recommended dosage. (b) (4) 
How Supplied	Tablets: • 20 mg white to light yellow, oblong-shaped, film-coated tablets debossed with " 772" on one side and "20" on the other side available as: o 2 x 20 mg tablets per blister card in secondary packaging (NDC 50242-828-02) • 40 mg white to light yellow, oblong-shaped, film-coated tablets debossed with "BXM40" on one side available as: o 2 x 40 mg tablets per blister card in secondary packaging (NDC 50242-860-02) For Oral Suspension: • XOFLUZA for oral suspension 40 mg/20 mL (2 mg/mL) are white to light yellow granules and are supplied in an amber glass bottle. When constituted with sterile water , the usable volume of suspension is 20 mL, equivalent to 40 mg of baloxavir marboxil. XOFLUZA for oral suspension are available as: o 40 mg/20 mL (2 mg/mL) for oral suspension: NDC 50242-583-01
Storage	Tablets: • Store XOFLUZA in its blister package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. For Oral Suspension:

	• Store granules at room temperature 20°C to 25°C (68°F to 77°F) and keep in the original bottle; excursions are permitted between 15°C and 30°C (59°F and 86°F). • Store constituted suspension no longer than (b) (4) hours at room temperature 20°C to 25°C (68°F to 77°F) when constituted with sterile water. The suspension must be discarded if not used within (b) (4) hours of preparation or if suspension has been stored above 25°C (77°F).
Container Closure	For Oral Suspension: amber glass bottle with child-resistant screw cap including tamper-evident ring

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 13, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 210854. Our search did not identify previous reviews with outstanding recommendations relevant to this review.

APPENDIX F. RESPONSE TO INFORMATION REQUESTS/LABELING COMMENTS

- Response to July 16, 2020 Information Request/Labeling Comments received on July 30, 2020, available at: \\CDSESUB1\evsprod\nda214410\0029\m1\us\response-label.pdf

- Response to July 21, 2020 Information Request/Labeling Comments received on July 30, 2020, available at: \\CDSESUB1\evsprod\nda214410\0029\m1\us\response-artwork.pdf

- Response to August 10, 2020 Information Request received on September 30, 2020, available at: \\CDSESUB1\evsprod\nda214410\0045\m1\us\request.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Xofluza labels and labeling submitted by Genentech, Inc.

- Container label received on July 30, 2020
- Carton labeling received on July 30, 2020
- Prescribing Information and Patient Package Insert (Image not shown) received on:
  - January 23, 2020, available from: \\CDSESUB1\evsprod\nda214410\0001\m1\us\clean-label-text.docx
  - September 4, 2020, available from: \\CDSESUB1\evsprod\nda214410\0040\m1\us\redlined-label-text.doc

G.2 Label and Labeling Images

- Container Label

(b) (4)

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[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S VAUGHAN
10/05/2020 10:46:09 PM

SEVAN H KOLEJIAN
10/05/2020 11:22:41 PM

Clinical Inspection Summary

Date	09/18/2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Christine Kim, Pharm.D., Regulatory Project Manager Melisse Baylor, M.D., Clinical Reviewer Mary Singer, M.D., Clinical Team Leader Division of Antiviral Products (DAVP)
NDA #	214410
Applicant	Genentech Inc.
Drug	Xofluza (Baloxavir Marboxil)
NME	No
Therapeutic Classification	Polymerase Acidic Endonuclease Inhibitor
Proposed Indications	1. Treatment of acute uncomplicated influenza in healthy pediatric patients 1 to < 12 years of age who have been symptomatic ≤ 48 hours (b) (4) 2. Post-exposure prophylaxis of influenza in patients ≥ 1 year of age (NDA 210854/S-004)
Consultation Request Date	02/13/2020
Initial Summary Goal Date	08/25/2020
Updated Summary Goal	09/22/2020
Action Goal Date	09/25/2020
PDUFA Date	11/23/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEDATIONS

The clinical investigators Drs. Baker, Yudovich, Matsuda, and Ono were inspected in support of this application. Based on the results of these inspections, the studies (Protocols CP40563 and 1719T0834) appear to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indications.

For Study 1719T0834, which was solely conducted in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) shared with OSI brief inspection reports (b) (4)

Based on PMDA's inspection reports, no issues of significant concern were found.

II. BACKGROUND

Xofluza (baloxavir marboxil) is a prodrug that is converted to an active form through hydrolysis, which selectively inhibits cap-dependent endonuclease activity necessary for replication of influenza viruses. It was initially approved by the FDA on October 24, 2018 for the treatment of acute uncomplicated influenza in patients 12 years of age and older who had been symptomatic for no more than 48 hours (NDA 210854). It was later approved on October 16, 2019 to treat patients

with acute uncomplicated influenza who are at high risk of developing influenza-related complications (NDA 210854-S001).

The applicant, Genentech Inc., submitted the data from a randomized, double-blind, active (oseltamivir)-controlled pediatric trial (Protocol CP40653) to assess the safety and efficacy of baloxavir marboxil in otherwise healthy pediatric patients 1 to < 12 years of age with influenza-like symptoms as well as a randomized, double-blind, placebo-controlled pediatric trial in Japan (Protocol 1719T0834) to evaluate the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection. The clinical investigator inspections of Drs. Baker, Yudovich, Matsuda, and Ono were conducted. The following described briefly the Protocols CP40563 and 1719T0834.

Protocol CP40563

Title: "A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients"

The primary study objective was to compare the safety and efficacy of a single dose of baloxavir marboxil compared with 5 days of oseltamivir administered twice daily for the treatment of influenza in pediatric patients 1 to <12 years of age.

The *primary efficacy endpoint* was Time to Alleviation of Influenza Signs and Symptoms (TTAS) which defined as the length of time taken from the start of treatment to the point at which all the following criteria were met and remained so for at least 21.5 hours:

- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms: items 14 and 15 of the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) questionnaire
- A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?"
- First return to afebrile state (tympanic temperature ≤37.2°C).

Protocol 1719T0834

Title: "A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection"

The primary study objective was to evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection in subjects who were household members (hereinafter referred to as "subjects") of influenza-infected subjects (hereinafter referred to as "index patients").

The *primary efficacy endpoint* was the proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

Rationale for Site Selection

The clinical investigator (CI) sites were selected primarily based on numbers of enrolled subjects, treatment effect, protocol deviations, and prior inspection history.

III. RESULTS

FDA Inspections and Assessments

1. **Jeffrey Baker, M.D.**
   Site #315110
   187 E 13th St #8262
   Idaho Falls, ID 83404
   Inspection dates: 26 May – 3 June 2020

At this site for Protocol CP40563, 19 subjects were screened and 16 were enrolled, all of whom completed the study.

The inspection reviewed the subject-specific records for the 16 enrolled subjects. These records included, but were not limited to, study eligibility, dosing, primary efficacy endpoint data (TTAS), subject disposition, adverse events, concomitant medications, and protocol deviations. Regulatory records reviewed included FDA Form 1572, financial disclosures, Independent Review Board (IRB) approvals, delegation logs, training records, drug accountability records, and monitoring reports.

The primary efficacy endpoint data in the subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted.

It was observed that an adverse event of "kidney infection" and the concomitant medication sulfatrim (as reported by the subject's mother) were not recorded in the case report form or reported to the sponsor. Specifically, according to the medical chart, Subject # (b) (6) (in baloxavir marboxil treatment group) had a "kidney infection" and took sulfatrim from (b) (6)

Reviewer's comment: We recommend that the review division consider this under reported adverse event when evaluating the safety profile of the study drug. Dr. Baker acknowledged that they missed reporting this adverse event and stated that they have already implemented quality assurance training as a preventive action.

2. **Martin Yudovich, M.D.**
   Site #317919
   4501 Groveway Drive
   Houston, TX 77087
   Bioavailability (BA)/bioequivalence (BE) inspection dates: 08-18 June 2020
   OP13 assessment dates: 1-3 July 2020

At this site for Protocol CP40563, a total of 35 subjects were screened and 30 were enrolled, and all of whom completed the study.

Following the selection of this site for GCP inspections, it turned out that a bioavailability

(BA)/bioequivalence (BE) inspection was conducted for this protocol that reviewed the study records for all 35 screened subjects. These records included, but were not limited to, informed consent, e-Diaries, eligibility, adverse events, the control and receipt of the Investigational Study Drugs, and documentation of the dosing of the active control drug (oseltamivir) and the study drug.

Therefore, the decision was made to conduct an investigation (in lieu of a full CI GCP site inspection) for this protocol at this site with the focus on the efficacy and safety data. The assessment reviewed 15 enrolled subjects for the primary efficacy endpoint data and safety data.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor and no discrepancies were noted. There was no evidence of underreporting of adverse events.

3. **Tadashi Matsuda, M.D.**
   Site # PMA
   9-106 Fujigaoka
   Kuwana City, Mie 511-0865
   Japan
   Remote Regulatory Assessment dates: 13-21 July 2020

A remote investigation (in lieu of a full CI GCP site inspection) was conducted for this site in Japan due to travel restrictions during the COVID-19 pandemic. Video conferencing via WebEx, document sharing via an online platform (box.com), and read-only access to the online trial master file were utilized for the assessment. At this site for Protocol 1719T0834, 19 subjects were screened, all of whom were enrolled and completed the study.

This investigation reviewed the records for all 19 screened subjects. These subject-specific records included, but were not limited to, screening and study eligibility, subject diaries, primary efficacy data, laboratory reports, adverse events, concomitant medications, protocol deviations, and individual drug dispensing logs. Regulatory documents reviewed included FDA Form 1572, financial disclosures, site visit log, screening and enrollment log, delegation log, correspondences between sponsor and Dr. Matsuda, and monitoring visit reports.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

4. **Ryuta Ono, M.D.**
   Site # PGB
   3-3-26 Miyamaedaira Miyamae-ku
   Kawasaki City, Kanagawa 216-0006
   Japan
   Remote Regulatory Assessment dates: 21-31 July & 3-4 August 2020

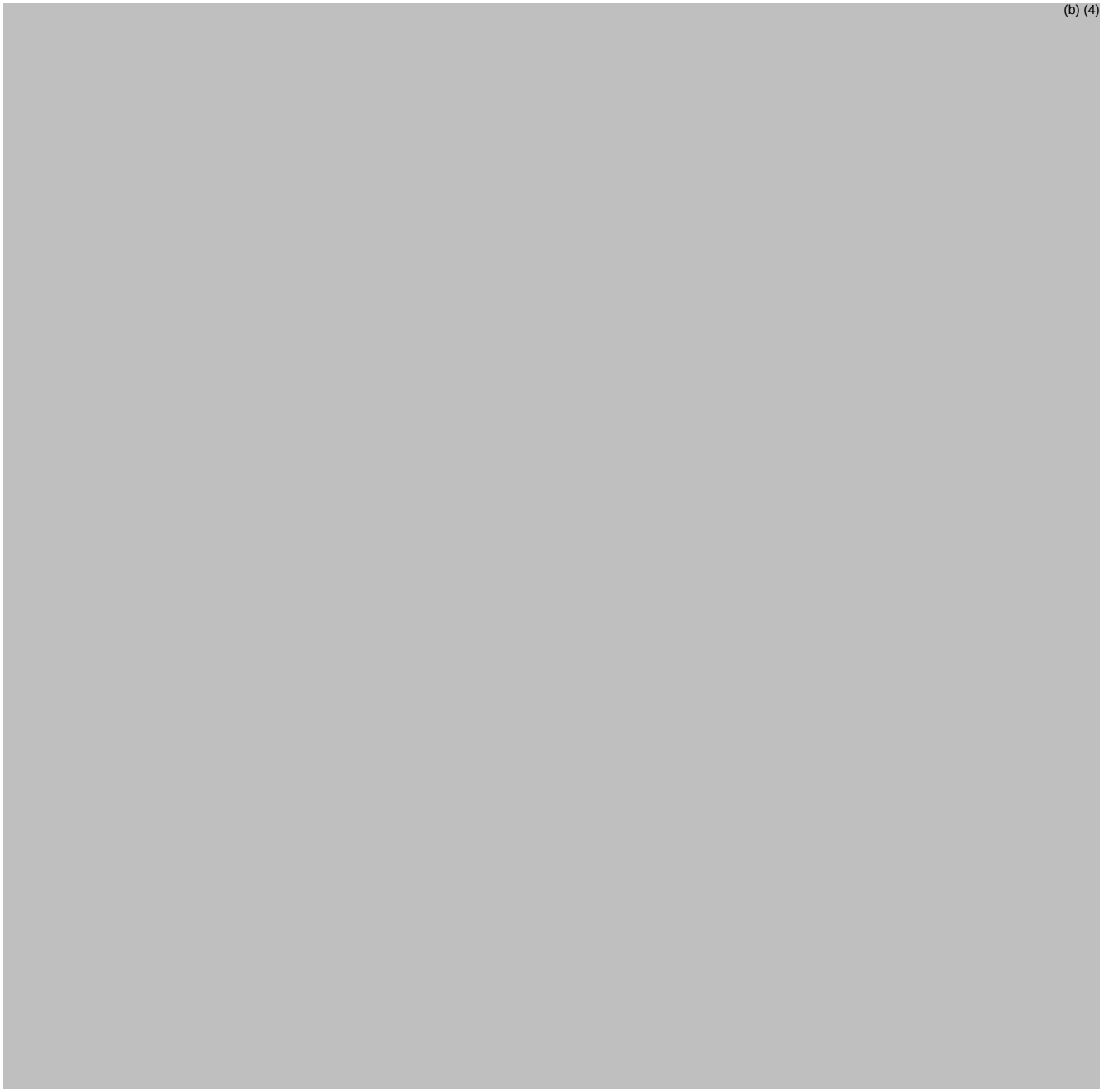
A remote investigation (in lieu of a full CI GCP site inspection) was conducted for this site in Japan due to travel restrictions during the COVID-19 pandemic. Video conferencing via WebEx, document sharing via an online platform (box.com), and read-only access to the online trial master file were utilized for the assessment. At this site for Protocol 1719T0834, 37 subjects were screened and 36 were enrolled, all of whom completed the study.

This investigation reviewed the records for all 36 enrolled subjects. These subject-specific records included, but were not limited to, screening and study eligibility, subject diary, primary efficacy data, adverse events, concomitant medications, protocol deviations, and individual drug dispensing logs. Regulatory documents reviewed included FDA 1572, financial disclosures, IRB approvals, delegation log, randomization/dosing, IP accountability/reconciliation, training records/ certifications, and laboratory accreditation.

The primary efficacy endpoint data in the subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

Additional Information: Review of Inspection Reports by Pharmaceuticals and Medical Devices Agency (PMDA) in Japan

(b) (4)



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Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
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cc:
Central Doc. Rm. NDA 214410
DAVP/Project Manager/Christine Kim
DAVP/Medical Officer/Melisse Baylor
DAVP/Clinical Team Leader/Mary Singer
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/s/

JENN W SELLERS
09/18/2020 05:48:09 PM

PHILLIP D KRONSTEIN
09/18/2020 06:34:36 PM

KASSA AYALEW
09/19/2020 10:29:12 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 9/18/2020

To: Christine Kim
Senior Regulatory Health Project Manager
Division of Antiviral Products (DAVP)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for XOFLUZA™ (baloxavir marboxil) tablets, for oral use

NDA: 210854 Supplement 4 (b) (4), 214410

In response to DAVP's consult request dated January 29, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for XOFLUZA™ (baloxavir marboxil) tablets, for oral use. This supplement proposes to update the clinical studies and indication of the PI to include the treatment of acute uncomplicated influenza in patients 1 years of age or older, who have been symptomatic for no more than 48 hours and are otherwise healthy, or at high risk of developing influenza-related complications. This supplement also includes post-exposure prophylaxis of influenza in patients 1 years of age or older following contact with an individual who has influenza.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on September 6, 2020, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

NIMA OSSAREH
09/18/2020 11:19:16 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 18, 2020
To:	Christine Kim, PharmD, RAC-US Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route, Application Type/Number, Supplement Number:	XOFLUZA (baloxavir marboxil) granules for suspension, for oral or enteral use, NDA 214410 XOFLUZA (baloxavir marboxil) tablets, for oral use, NDA 210854/S-004 (b) (4)
Applicant:	Genentech Inc.

1 INTRODUCTION

On January 23, 2020, Genentech Inc. submitted for the Agency's review an original New Drug Application (NDA) 214410 for XOFLUZA (baloxavir marboxil) granules for suspension with the following proposed indications:

- for the treatment of acute uncomplicated influenza in otherwise healthy patients 1 year of age and older who have been symptomatic for no more than 48 hours.
- for the post-exposure prophylaxis of influenza in patients 1 year of age and older.

The Applicant also submitted Prior Approval Supplements (PAS) – Efficacy to their approved NDA 210854/S-004 (b) (4) for XOFLUZA (baloxavir marboxil) tablets to update the Prescribing Information (PI) with the aforementioned indications and formulation as the NDAs will share the same PI and Patient Package Insert (PPI).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on January 29, 2020, for DMPP and OPDP to review the Applicant's proposed PPI for XOFLUZA (baloxavir marboxil) granules for suspension and XOFLUZA (baloxavir marboxil) tablets.

2 MATERIAL REVIEWED

- Draft XOFLUZA (baloxavir marboxil) granules for suspension and XOFLUZA (baloxavir marboxil) tablets PPI received on January 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 8, 2020.
- Draft XOFLUZA (baloxavir marboxil) granules for suspension and XOFLUZA (baloxavir marboxil) tablets Prescribing Information (PI) received on January 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 8, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I MAYROSH
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NIMA OSSAREH
09/18/2020 11:58:38 AM

LASHAWN M GRIFFITHS
09/18/2020 12:18:50 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/30/2020

TO: Division of Antiviral Products
Office of Infectious Diseases

FROM: Division of Generic Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214410

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not able to be conducted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Although OSIS has no inspection history for the sites, travel to Japan is not currently allowed. On January 30, 2020, the World Health Organization (WHO) determined the rapidly spreading outbreak of the novel coronavirus, SARS-CoV-2, that causes the disease, COVID-19, constitutes a Public Health Emergency of International Concern.

These sites are located in a country where official travel is discouraged by US State Department.

Therefore, OSIS determined that an inspection of the studies conducted at the sites is not possible at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Houeikai Medical Corp., Sekino Clinical Pharmacology Clinic	3-28-3 Ikebukuro, Toshima-ku, Tokyo, Japan
Analytical	(b) (4)	

James J. Lumalcuri -S

Digitally signed by James J. Lumalcuri -S
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Date: 2020.03.30 13:09:58 -04'00'

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/s/

JAMES J LUMALCURI
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