CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210854Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210854
PDUFA Goal Date	10/24/2018
OSE RCM #	2018-847
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	09/28/2018
Subject	Evaluation of the Need for a REMS
Established Name	Baloxavir
Trade Name	Xofluza
Name of Applicant	Genentech USA
Therapeutic class	Antiviral; Polymerase acidic (PA) endonuclease inhibitor
Formulation	20 mg and 40 mg oral tablets
Dosing Regimen	40-80kg single dose 40mg by mouth; At least 80kg: single dose 80mg

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xofluza (baloxavir marboxil) is necessary to ensure the benefits outweigh its risks. Genentech USA submitted a New Drug Application (NDA) 210854 for baloxavir marboxil with the proposed indication 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. The serious risk associated with baloxavir marboxil is one that will be communicated in the warning and precaution section of the product label alerting prescribers not to use this product for any illness caused by pathogens other than the influenza virus. The applicant did not submit a proposed REMS or risk management plan with this application.

Given the adverse events associated with baloxavir (and other antiviral treatments approved for the influenza virus) that are already known to the prescribing community, and the duration of treatment being a single, one-time dose, DRISK and the Division of Antiviral Products agree that a REMS is not necessary for approval of baloxavir marboxil.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Xofluza (baloxavir marboxil) is necessary to ensure the benefits outweigh its risks. Genentech USA submitted a New Drug Application (NDA) 210854 for baloxavir marboxil with the proposed indication 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. The risk associated with baloxavir marboxil is one warning and precaution to not use this product for any illness caused by pathogens other than the influenza virus. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Baloxavir marboxil is an antiviral drug with activity against influenza virus. Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, which is the active form that exerts its anti-influenza activity by inhibiting an influenza virus-specific enzyme, endonuclease polymerase acidic protein.[1,a] The drug is indicated 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, to be given as a single, one time dose. In patients that weigh 40-80 kg the dose is 40 mg to be taken orally in a single dose with or without food, and for patients weighing 80 kg or greater, the dose is 80 mg to be taken orally in a single dose with or without food. Co-administration with polyvalent cation containing products may decrease plasma concentrations of baloxavir which may reduce the efficacy of baloxavir marboxil. Recommendations are to avoid taking this medication with polyvalent cation containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, or magnesium.[1,2]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Baloxavir marboxil is an NME and is expected to be prescribed by a wide variety of physicians and/or midlevel providers to patients in an ambulatory care setting.[b] Baloxavir marboxil was granted Priority Review and is currently not marketed in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210854 relevant to this review:

- 01/21/2016: IND 126653 acknowledged for baloxavir marboxil under Shionogi Pharmaceuticals
- 11/18/2016: Change in ownership of IND 126653 from Shionogi Pharmaceuticals to Genentech/Roche USA
- 04/24/2018: NDA 210854 submission for baloxavir marboxil received
- 08/28/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for baloxavir marboxil

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Influenza (flu) is a contagious respiratory illness caused by influenza viruses A and B, that occurs in outbreaks that vary in severity from approximately the beginning of the fall season throughout the winter, with peak activity in the United States usually in February.[3,c] Symptoms of the flu commonly include respiratory involvement such as cough, sore throat, runny or stuffy noses, in addition to body aches, fatigue, and fever (which may or may not be present). The Centers for Disease Control (CDC) estimates that influenza has resulted in between 9.2 million and 35.6 million illnesses, between 140,000 and 710,00 hospitalizations and between 12,000 and 56,000 deaths each year since 2010.[3,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Recommendations from the CDC as a first line preventive measure from getting the flu are to get a flu vaccine, while antiviral drugs are a second line of defense to treat the flu. Antiviral drugs may lessen he symptoms and shorten the time a patient remains ill, depending on when antiviral therapy was given. Data suggest that these drugs may lessen the symptoms and time with the flu by 1 day if therapy is initiated within two days of contracting the influenza virus.[3] Oseltamivr (Tamiflu®), zanamivir (Relenza®) and peramivir (Rapivab®) are the only FDA approved antiviral drugs recommended to treat the flu this

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

season.[3] The table below is a summary of the safety profile of the currently FDA approved antivirals recommended for treatment of the Influenza viruses.

Table 1: Summary of Treatment Options for the Influenza Virus in the United States

Trade Name	Generic Name	Year Approved	Antiviral Class	Dosing/Administration	Safety/Labeling
Tamiflu[4]	Oseltamivir	1999	Neuraminidase inhibitor	Prevention: 75mg once daily for at least 10 days; pediatric patients 1 to 12 years of age is based on weight Treatment: 75mg twice daily for 5 days in adults and adolescents 13 years and older. Dosing is weight based in children under 13 years of age and for renally impaired patients	Skin/hypersensitivity reactions such as Stevens-Johnson syndrome (5.1) Neuropsychiatric events (5.2)
Relenza[5]	Zanamivr inhalation powder	1999	Neuraminidase inhibitor	Prophylaxis: 10mg once daily for 10-28 days Treatment: 10mg twice daily for 5 days	Bronchospasm (5.1) Allergic reactions (5.2) Neuropsychiatric Events (5.3) Use in caution in patients with underlying lung disease (5.4) Medication Guide and Instructions for Use
Rapivab[6]	Peramivir injection for intravenous (IV) use	2014	Neuraminidase inhibitor	Administer 600mg IV as a single dose in adults/adolescents 13 years or older. 12mg/kg in patients 2 to 12 years of age	Anaphylaxis and serious skin reactions such as Stevens Johnson Syndrome (5.1) Neuropsychiatric events (5.2)

None of the medications approved for the treatment of influenza were approved with a Boxed Warning or REMS. Baloxavir marboxil exerts its pharmacological activity in the replicative phase of the influenza life cycle by inhibiting endonuclease activity, a different mechanism of action than what is in the currently approved treatment armamentarium. As noted above, these drugs belong to the neuraminidase inhibitor (NAI) class of antivirals, which primarily exert their action near the end of viral replication. Resistance has also been reported in some literature with the NAI's which have varying rates of resistance from 0.6% to 2.9% in adults, and as high as 10.9% in children.[2]

4 Benefit Assessment[1]

The Applicant submitted two randomized, controlled, double-blinded, clinical trials to support the approval of this NDA. These trials were conducted in two different influenza seasons in patients with uncomplicated influenza who were otherwise healthy.

> **Trial 1**: Trial 1 was a placebo-controlled dose finding study. There were 400 adult patients aged 20 to 64 who received a single dose of baloxavir marboxil compared with placebo. All of the patients in this trial were Asian, 62% were male, and the mean age was 38 years. Influenza A/H1N1 was the predominant strain in 63% of patients, followed by influenza B, and influenza A/H3N2.
>
> **Trial 2:** This was a phase 3 active and placebo-controlled trial, where baloxavir marboxil was studied in 1,436 adult and adolescent patients. In this trial, patients weighing less than 80 kg were enrolled and received a dose of 40 mg while patients weighing 80 kg or more were given 80 mg as a single one-time oral dose. Most patients in this trial were Asian (78%), and the mean age was 34 years. Ninety percent of patients had influenza A/H3N2 as the predominant strain. Adults ages 20 to 64 years received baloxavir marboxil or placebo as a single oral dose on Day 1 or oseltamivir twice a day for 5 days. Patients in the baloxavir marboxil and placebo arms received a placebo for the duration of oseltamivir dosing after baloxavir marboxil dosing was completed in that arm. Adolescent patients 12 to less than 20 years of age received baloxavir marboxil or placebo as a single oral dose.

The primary endpoint of both trials was time to alleviation of symptoms which was defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) were reported by the patient as none or mild for at least 21.5 hours.

In Trial 1, the time to alleviation of symptoms was statistically significantly shorter in patients who received baloxavir marboxil (50 hours; (95% confidence interval of 45, 64) compared to placebo (78 hours; confidence interval 68, 89).

In Trial 2, adolescent patients (age 12 to 17) had a statistically significant shorter time to alleviation of symptoms who received baloxavir marboxil; 54 hours (95% confidence interval of 43, 81) compared to 93 hours (95% confidence interval of 64, 118) in the placebo arm. However, when baloxavir was compared to oseltamivir, there was no difference in the time to alleviation of symptoms between patients who received baloxavir marboxil (54 hours) and those who received oseltamivir (54 hours).

The clinical virology reviewer recommends approval for the treatment of acute uncomplicated influenza virus infection in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Since there was limited data provided in for efficacy against the influenza type B virus, the reviewer recommends Limitations of Use in the label to state that the data submitted do not demonstrate a consistent treatment effect in patients infected with influenza type B virus.[7,e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions[1,f]

The safety profile of baloxavir marboxil is based on data from 2 placebo-controlled trials, in which a total of 910 patients received the study drug. Of these, 710 patients received baloxavir at the recommended dose. Adverse events (regardless of causality assessment) that was reported in at least 1% of adult and adolescent patients who received baloxavir marboxil at the recommended dose included: diarrhea (3%), bronchitis (2%), nasopharyngitis (2%), and nausea (1%). These adverse events did not appear to be reported more frequently with baloxavir marboxil as compared to placebo.

Clinical safety presentations at the internal midcycle meeting revealed that there were no safety issues identified, and additional safety analyses will be performed.[8] At the time of this writing, labeling negotiations were still ongoing. There are no boxed warnings that are being considered in the labeling for baloxavir marboxil, and at this time, there is only one Warning and Precaution noted in the label.

5.1 RISK OF BACTERIAL INFECTIONS

If approved, the label will advise in the warning and precaution section that serious bacterial infections may begin with influenza-like symptoms, may co-exist with or occur as a complication of the flu. Recommendations will be to use baloxavir marboxil only as primary treatment for the flu virus, and that prescribers should be cognizant of potential secondary bacterial infections and treat those infections as appropriate.

6 Expected Postmarket Use

Baloxavir marboxil is expected to be prescribed by a wide variety of physicians and midlevel healthcare providers to patients in the ambulatory care setting. (b) (4)

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for baloxavir marboxil beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of baloxavir marboxil for the proposed indication, and at this time there are no major safety issues identified.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Influenza is an acute, highly contagious respiratory illness that contributes to several cases of infections each year. Baloxavir marboxil is an antiviral drug with a novel mechanism of action with the proposed indication as treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. The duration of treatment with baloxavir marboxil is a single oral dose. There are currently three FDA approved treatments recommended by the CDC to treat influenza virus. None of these products were approved with a Boxed Warning or REMS, and when compared to the safety profile of baloxavir, there were no adverse events that appear to be abnormal or unknown to the expected prescribing community.

Given the adverse events associated with baloxavir (and other antiviral treatments approved for the treatment of influenza) that are already known to the prescribing community, and the duration of treatment being a single, one-time dose, DRISK and the Division of Antiviral Products agree that a REMS will be necessary for approval of baloxavir marboxil.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of baloxavir marboxil outweigh the risks. In general, healthcare providers who treat influenza are familiar with the adverse events of influenza medications and the importance of patient monitoring. Should the Division of Antiviral Products have any concerns or questions or if new safety information becomes available that may necessitate the need for a REMS, please send a consult to DRISK.

10 Appendices

10.1 References

[1] Baloxavir draft labeling, September 14, 2018

[2] Baloxavir Marboxil Clinical Overview, Genetech USA

[3] www.cdc.gov/flu/keyfacts.htm accessed 9/14/2018

[4] Tamiflu US Prescribing Information. Revised April 2018, Genentech, Inc.

[5] Relenza US Prescribing Information. Revised 2018, Glaxo Smithkline

[6] Rapivab US Prescribing Information. Updated 2017, BioCryst Pharmaceuticals

[7] Ince W and Thomson M. NDA 210854 Baloxavir Marboxil Clinical Virology Review, submitted in DARRTS September 24, 2018

[8] Clinical and Statistical Mid-Cycle Meeting Presentations NDA 210854 baloxavir marboxil, July 24, 2018

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/s/

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