CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214410Orig2s000
210854Orig1s005,s009

OTHER ACTION LETTERS

NDA 214410/Original 2
NDA 210854/S-05
NDA 210854/S-09

COMPLETE RESPONSE

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 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 Federal Food, Drug, and Cosmetic Act for XOFLUZA (baloxavir marboxil) 20 mg and 40 mg tablets.

The aforementioned applications provide for:

NDA 214410/Original 2	The use of XOFLUZA (baloxavir marboxil) for oral suspension, for the treatment and post-exposure prophylaxis of influenza in pediatric patients 12 months to less than 12 years of age
NDA 210854/S-05	The use of XOFLUZA (baloxavir marboxil) tablets for the treatment of influenza in pediatric patients 12 months to less than 12 years of age
NDA 210854/S-09	The use of XOFLUZA (baloxavir marboxil) tablets for post-exposure prophylaxis of influenza in pediatric patients 12 months to less than 12 years of age

We have completed our review of these applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL and CLINICAL VIROLOGY

While the frequency of treatment-emergent resistance in adult and adolescents has ranged between approximately 3% and 11% in clinical trials, treatment-emergent

resistance in subjects less than12 years of age in clinical trials reviewed to date has been consistently observed in approximately 22% or more of subjects with higher frequencies observed in type A and A/H3N2 subsets. Additional preliminary top-line data from trial T0835 indicate frequencies of treatment-emergent resistance ranged up to 44% overall, and up to 75% in A/H3N2 virus in pediatric patients less than 12 years of age. Treatment-emergent resistance is associated with virus rebound, prolonged shedding, and potentially prolonged contagiousness. The Division concluded that because there is a substantially elevated risk of resistance in children less than 12 years old, with frequencies potentially up to 75%, additional data are needed to assess the risk of transmission of resistant virus to household or community contacts from the pediatric population, as transmitted resistant virus may limit treatment options for contacts who become infected and perhaps contribute to widespread circulating baloxavir resistance. Sporadic cases of transmitted baloxavir resistance have been reported to date, but there is currently no evidence of widely circulating resistance to baloxavir. The risk, however, of circulating baloxavir-resistant influenza virus may increase if baloxavir marboxil becomes widely used in the pediatric population less than 12 years of age.

In order to address these concerns, the Applicant should submit data from Trial MV40618 entitled, “A Phase IIIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Clinical Efficacy Study of Baloxavir Marboxil for the Reduction of Direct Transmission of Influenza from Otherwise Healthy Patients to Household Contacts”, in order to adequately evaluate the risk of transmission of baloxavir resistant influenza virus from treated index patients, including those less than 12 years of age. Additionally, the Applicant should submit the complete clinical study report and datasets from Study T0835 for full evaluation of resistance in that study.

PRESCRIBING INFORMATION

(1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original/supplemental application data.
- Include tables that compare frequencies of adverse events in the original and supplemental applications with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original /supplemental application data.

[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

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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