CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210875

COMPLETE RESPONSE

Sunovion Pharmaceuticals Inc.
Attention: Sonya A. Roeloffzen
Director, Global Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Roeloffzen:

Please refer to your New Drug Application (NDA) dated March 29, 2018, received March 29, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Kynmobi (apomorphine) sublingual film 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg.

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

HUMAN FACTORS (HF)

As communicated to you in a November 21, 2018, Discipline Review (DR) letter, the human factors (HF) validation study conducted for Kynmobi does not provide sufficient evidence to demonstrate that the proposed product can be used safely and effectively by intended users for its intended uses and use environments. Your HF study identified several use errors and close calls that occurred on critical tasks. Additionally, you have not provided data to demonstrate that your proposed mitigations are effective and do not introduce new use-related risks. Furthermore, your HF study did not evaluate the final intend-to-market user interface, i.e., your proposed (b) (4) packaging. Thus, you have not provided sufficient data to demonstrate whether the intended users can open and close the packaging.

We acknowledge your December 7, 2018, formal response to the DR letter, and note that your response provided additional information and your plan to address the Agency's concerns about your human factors (HF) validation study results and the (b) (4) packaging. We also acknowledge that you have evaluated this product in the clinical environment. However, the intend-to-market outer carton (b) (4) packaging) was not part of the user interface evaluated in the HF validation study. While we acknowledge your proposed plan to submit a petition for exemption from the child-resistant (CR) packaging requirement post-approval (b) (4) (b) (4), it is not clear whether such exemption will be granted.

The specific deficiencies identified in your HF validation study include the following:

1. Your study results showed several use errors and close calls that occurred on critical tasks. We note that you implemented revisions to the Instructions for Use (IFU) and film pouch (container label) to address the use errors and close calls. However, you did not validate the revisions to the user interface. Furthermore, our evaluation of the proposed user interface, label and labeling identified areas of vulnerability that may lead to medication errors, and we provided additional recommendations in our November 21, 2018, Discipline Review letter. We acknowledge that you have implemented our IFU, container label, and carton labeling recommendations.

2. We note that the (b) (4) packaging requires a push-pull technique to open, which may pose concerns for the intended user population (i.e., patients with Parkinson's disease) due to dexterity and motor impairments that occur in the OFF period. We also note that Kynmobi is intended for the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease; therefore, delay in therapy (e.g., due to difficulty opening the (b) (4) packaging) would cause the user to remain in the OFF state. We are concerned that if users experience difficulty opening or closing the (b) (4) packaging, they might remove the foil pouches from the packaging permanently or alter the packaging to eliminate the child-resistant features, which may increase the risk of secondary exposure. As the (b) (4) packaging was not part of the user interface evaluated in the HF validation study and the intended user population has clinical manifestations that might impact interaction with the (b) (4) packaging, we find that the study results are not representative of real-world use.

A human factors validation study using the intend-to-market user interface (i.e., (b) (4) packaging) is needed to demonstrate that the mitigations are effective and do not introduce new risks. You should evaluate the use-related errors observed in the HF study, employ additional mitigation strategies, and update your use-related risk analysis prior to conducting that study.

We recommend you submit your HF validation study protocol for feedback before commencing your study. Note that submission of a protocol for review is not a requirement.

Please refer to our draft guidance titled "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" for the content of a human factors validation study protocol submission. The guidance is available online at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in: Applying Human Factors and Usability Engineering to Medical Devices, available online at:

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

> Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
> http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf
>
> Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
> http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Complete Study CTH-203 and provide the final report for Study CTH-203, which is necessary to justify the relevance of comparative data with your proposed product (Kynmobi) and Apo-go to support the scientific appropriateness of reliance on FDA's finding of safety for Apokyn. In addition, clearly describe the data and information that supports the scientific bridge between your proposed product (Kynmobi) and the listed drug relied upon (Apokyn), which may include data and information supporting a bridge between Kynmobi and Apo-go and between Apokyn and Apo-go.

SAFETY

You have not adequately characterized the oropharyngeal adverse events that were observed in patients treated with Kynmobi. These events were reported under multiple terms, such as oropharyngeal pain, oropharyngeal swelling, pharyngeal erythema, gingivitis, oral pain, lip swelling, gingival edema, mouth edema, lip ulceration, oral mucosal erythema, stomatitis, mouth ulceration, oral discomfort, oral hypoesthesia, mouth swelling, glossodynia, tongue discomfort, lip blister, dysgeusia, angular cheilitis, oropharyngeal pain, leukoplakia oral, lip exfoliation, oral mucosal blistering, agueusia, throat irritation, oral allergy syndrome, pharyngeal edema, soft palate swelling, and others.

Taken together, and according to our analyses, oropharyngeal adverse events were reported in over 25% of patients treated with Kynmobi in the maintenance phase of Study 300, compared to 4% of patients on placebo. Oropharyngeal adverse events were also commonly observed in Study 301, and were a common reason for discontinuation in both studies.

You will need to provide a comprehensive discussion and summary of oropharyngeal adverse events with Kynmobi, including an expert review from a qualified dermatologist. For both Study 300 and Study 301, reexamine your safety database, and pool all related oropharyngeal adverse events in appropriate clusters (e.g., oropharyngeal edema, pain, ulceration, hypoesthesia, etc.). Identify the number of oropharyngeal adverse events, and the number of unique patients reporting at least one of the adverse events in the cluster. Identify the number of discontinuations in both studies for each of these events and each cluster of events. Provide analyses of these events by severity. Present this information for each study phase (e.g., titration and maintenance) and for all patients in the overall safety population. Present analyses of the time to onset of the events after treatment initiation, evolution, time course, time to resolution after treatment discontinuation, and relationship to the dose of Kynmobi. Present analyses of the association between oropharyngeal adverse events and systemic hypersensitivity, including the temporal relationship between oropharyngeal and systemic hypersensitivity events, if any.

Send all patients reporting new oropharyngeal adverse events in ongoing Study CTH-301 to a qualified dermatologist, and obtain photographs of all relevant oral and skin abnormalities associated with the event. Submit a copy of the dermatologist's diagnosis, the investigator's assessment, a case summary and the photographs of the relevant abnormalities.

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 application data.
    - Include tables that compare frequencies of adverse events in the original application 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.

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