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.

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 application data.

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.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. You will need to conduct in vitro studies to evaluate drug-drug interaction (DDI) potential of the two major metabolites from Kynmobi, apomorphine glucuronide and norapomorphine glucuronide.

2. For the ISS, submit a new set of ADaM datasets that are fully compliant with the CDISC standard. For example, the USUBJID should be uniform throughout the submitted data, with every patient in the development program having the same unique identifier in every dataset. The datasets should include all patients in the safety population from initiation of clinical studies through an appropriate cut-off date for your re-submission.

3. The Summary of Clinical Safety should be updated with attention to all adverse events of special interest, especially those suggesting hypersensitivity reactions. Perform an analysis by dose and duration of exposure until the time of AE development in cases identified by MedDRA SMQ for hypersensitivity and angioedema.

4. In addition to updating the analysis of exposure by total daily dose, perform an analysis of exposure to APL-130277 for Studies 300 and 301 using self-reported daily frequency of administration by patients.

5. For open-label Study CTH-301, submit the complete report or an interim report, if the study is still ongoing at the time of resubmission.

6. In the 120-Day Safety Update, the EXDOSFRQ (Dosing Frequency per Interval) column in the ADEX dataset is blank. Please provide this information in the amended datasets, using the information from the patient dosing diaries prior to each visit. List the doses

taken per day as 0 through 5. Add a DOSEON column to show the dose prescribed for the patient for each interval and another column showing the number of daily diaries returned for the interval (e.g., 0, 1 or 2).

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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jack Dan, Regulatory Project Manager, at (240) 402-6940.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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/

ERIC P BASTINGS
01/29/2019 09:33:29 PM