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APPLICATION NUMBER:

210875Orig1s000

SUMMARY REVIEW

Summary Review

Date	5/21/20
From	Gerald D. Podskalny, DO, and Eric Bastings, MD
Subject	Summary Review
NDA/BLA # **Supp #**	210875 Response to CR letter
Proprietary / Established (USAN) names	Kynmobi / Apomorphine hydrochloride sublingual film
Dosage forms / strength	Sublingual film / 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Proposed Indication(s)	Acute, intermittent treatment of "off' episodes in patients with Parkinson's disease
Action	Approval

1. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Sunovion Pharmaceuticals Inc. (Applicant) submitted a response to the complete response letter that was issued by the Agency on January 29, 2019, for their new drug application (NDA) for Kynmobi (apomorphine hydrochloride) sublingual film.

The proposed indication for Kynmobi is the acute, intermittent treatment of "off" episodes in patients with Parkinson's disease (PD). This 505(b)(2) NDA relies on nonclinical and clinical pharmacology information from listed drug Apokyn (NDA 21-264). Apokyn is approved for the treatment of "acute, intermittent treatment of hypomobility, off episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease.

As discussed in the summary review for the original application, the applicant conducted a relative bioavailability study (CTH-200) designed to bridge Kynmobi and Apo-go, an apomorphine subcutaneous injection marketed outside of the United States. The applicant also submitted in the original application interim results of a relative bioavailability study (CTH-203) between Apokyn, Apo-go and Kynmobi that was ongoing at the time. In addition, the applicant attempted to establish sameness between Apo-go and Apokyn based on composition and in vitro data.

The original application was issued a complete response (CR) letter because of deficiencies in human factors evaluations, inadequate bridging to listed drug Apokyn, and inadequate characterization of the oropharyngeal adverse events that were observed in patients treated with Kynmobi.

This new submission includes the applicant's response to the deficiencies listed in the CR action letter and to various issues that did not affect approvability of the original NDA.

Of note, the efficacy of Kynmobi was established in the first review cycle.

2. Chemistry, Manufacturing and Controls

Leah W. Falade, Ph.D. (Primary Reviewer), Ta-Chen Wu, Ph.D. (Secondary Reviewer), and Martha Heimann, Ph.D. (Technical Lead) reviewed the CMC information.

There are no outstanding product quality issues precluding approval.

3. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology review team included Mariam Ahmed, Ph.D. (Primary Reviewer), Sreedharan Sabarinath, Ph.D. (Team Lead), and Mehul Mehta, Ph.D. (Division Director).

505(b)(2) bridge

As discussed in the first-cycle summary review, insufficient information was provided by the applicant to establish a bridge between Kynmobi and Apokyn. The final results of relative bioavailability Study CTH-203 were needed to support the scientific bridge between the listed drug and Kynmobi. This new submission includes the final study report for Study CTH-203. The study shows that following the maximum recommended dose of Kynmobi (i.e., 30 mg), the extent of apomorphine exposure and Cmax is at least 10% and 40% lower, respectively, than following a 6-mg dose of Apokyn. Therefore, the OCP review team concludes that an acceptable bridge has been established between Kynmobi and Apokyn, allowing to rely on Apokyn's nonclinical safety information, and on applicable clinical pharmacology information from Apokyn.

Apomorphine metabolites

The Agency recommended that the applicant conduct in vitro studies to evaluate the drug-drug interaction (DDI) potential of two major inactive metabolites of Kynmobi, apomorphine glucuronide and norapomorphine glucuronide. The applicant submitted results from DDI studies of apomorphine glucuronide. The DDI potential of apomorphine glucuronide (through inhibition of major transporters) is considered minimal.

A postmarketing requirement will be issued to conduct in vitro studies to evaluate the DDI potential of the norapomorphine glucuronide major metabolite as a perpetrator for major CYP enzymes and transporters.

Office of Study Integrity and Surveillance (OSIS) inspections

Two clinical study sites and the analytical laboratory facility ((b) (4)) were inspected by the Office of Study Integrity and Surveillance (OSIS). The data from Study CTH-203 were found to be reliable.

Recommendation

The Office of Clinical Pharmacology recommends approval.

4. Clinical

Kenneth Bergmann, MD, was the primary clinical reviewer for the original NDA submission, and for the submission under review.

The efficacy of Kynmobi for the acute, intermittent treatment of "off" episodes was established during the first NDA review cycle.

The applicant did not adequately characterize in the original application the oropharyngeal adverse events that were observed in patients treated with Kynmobi. The applicant was requested 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 (controlled efficacy study) and Study 301 (open-label safety study), the applicant was asked to reexamine the safety database, and pool all related oropharyngeal adverse events in appropriate clusters (e.g., oropharyngeal edema, pain, ulceration, hypoesthesia, etc.).

The applicant was also requested to 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. In addition, the applicant was asked to present analyses of the association between oropharyngeal adverse events and systemic hypersensitivity, including the temporal relationship between oropharyngeal and systemic hypersensitivity events, if any. All patients reporting new oropharyngeal adverse events in Study 301, which was ongoing during the first review cycle, were to be examined by a qualified dermatologist/dentist with photographs taken of all relevant oral mucosal and skin abnormalities needing to be included in a case summary.

New safety information was added for 105 patients, who were treated between the 120-day update cut off (May 10, 2018) and the cutoff date for the resubmission (May 10, 2019).

The size of the overall safety database of Kynmobi is adequate. As Kynmobi is an intermittent-use drug intended to be taken during an acute "off" episode, the number of daily uses of the drug varies from day to day. The applicant could only provide daily dosing as an average daily dose (Table 1). Most patients took an average 0-2 doses of Kynmobi per day. The available safety information is limited for doses greater than 30 mg, which will be the highest recommended dose.

Table 1. Imputed average number of doses per day by highest dose level recorded during the maintenance phase of Study 300 and 301

APL-130277 Dose level	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	≥5	Total N
10 mg	36	20	5	2	1	0	64
15 mg	44	23	10	4	2	0	83
20 mg	37	27	8	3	2	0	77
25 mg	26	24	6	6	2	1	65
30 mg	16	14	4	3	0	0	37
35 mg	18	7	4	1	1	0	31
Total	177	115	37	19	8	1	357

Source: FDA Clinical Review

There is no significant new safety information related to deaths, serious adverse events and adverse dropouts in additional patients presented in this submission.

In the original submission, oropharyngeal adverse events were reported in an excessively granular fashion. Often, adverse events describing similar symptoms were presented as different preferred terms (e.g., oropharyngeal swelling and pharyngeal edema). The applicant was asked to reexamine the safety database, and pool all related oropharyngeal adverse events in appropriate clusters. The clinical review team also reanalyzed the applicant's safety data (Table 2). Terms for similar oropharyngeal adverse reactions were combined into clusters of related preferred terms (see Table 2) for oropharyngeal swelling, pain/paresthesia, and ulceration. Each patient was counted only once in a cluster, in each study phase.

Nausea and somnolence were the most common adverse reactions during the titration and the maintenance phase. Oral soft tissue swelling (lips, tongue, gingiva, and mouth) was reported as adverse reaction in 15% of patients treated with Kynmobi during the maintenance phase of Study 300, compared with 0% of patients who received placebo; 11% of patients discontinued Kynmobi because of this event.

Swelling of the face, oral allergy syndrome, hypersensitivity, or urticaria were reported as an adverse reaction in 6% of patients treated with Kynmobi during the maintenance phase of Study 300, compared with 0% of patients who received placebo; 4% of patients discontinued Kynmobi because of this event.

During the titration phase of Study 300, oral mucosal ulceration or stomatitis were reported as adverse reactions in 2% of patients treated with Kynmobi. During the maintenance phase of Study 300, oral mucosal ulceration or stomatitis were reported as adverse reactions in 7% of patients treated with Kynmobi, compared with 0% of patients who received placebo. During the titration of Study 300, oral soft tissue pain or paresthesia were reported as adverse reactions in 2% of patients treated with Kynmobi. During the maintenance phase of Study 300, oral soft tissue pain or paresthesia were reported as adverse reactions in 13% of patients treated with Kynmobi, compared with 2% of patients who received placebo.

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