CENTER FOR DRUG EVALUATION AND RESEARCH

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.

In general, oral mucosal irritation reactions were mild to moderate severity, and usually resolved with treatment discontinuation.

Table 2: Adverse reactions reported in at least 5% of patients treated with Kynmobi and with an incidence greater than placebo in Study 300 (Titration and Maintenance Phase)

	Titration	Maintenance	
	Kynmobi (N=141) %	Kynmobi (N=54) %	Placebo (N=55) %
Gastrointestinal disorders			
Nausea	21	28	4
Oral/pharyngeal soft tissue swelling[1]	1	15	0
Oral/pharyngeal soft tissue pain and paraesthesia[2]	2	11	2
Oral ulceration and stomatitis[3]	3	7	2
Oral mucosal erythema	4	7	4
Vomiting	4	7	0
Dry mouth	1	6	0
Nervous system disorders			
Somnolence	11	13	2
Dizziness	11	9	0
Headache	8	6	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	6	7	0
General disorders and administration site conditions			
Fatigue	3	7	0
Chills	6	4	0
Injury, poisoning and procedural complications			
Fall	4	6	2
Skin and subcutaneous tissue disorders			
Hyperhidrosis	4	6	4
Injury, poisoning and procedural complications			
Laceration	1	6	0
Immune system disorders			
Hypersensitivity[4]	0	6	0

[1] Includes lip swelling, lip edema, oropharyngeal swelling, gingival edema, edema mouth, swollen tongue, and pharyngeal edema
[2] Includes throat irritation, glossodynia, oral paresthesia, oral pain, oropharyngeal pain, gingival pain, and oral hypoesthesia
[3] Includes lip ulceration, oral mucosal blistering, cheilitis, stomatitis, and tongue ulceration
[4] Includes hypersensitivity, swelling face, oral allergy syndrome and urticaria

Evolution of oral/pharyngeal adverse events

Figure 1 and Figure 2 show the prevalence of oropharyngeal adverse events and the prevalence of hypersensitivity-related adverse events as a percent of the safety population over time. Reports of mild to moderate oropharyngeal adverse events started in the first week of treatment. The prevalence, shown as a percentage of the study population, remained under 10% until Week 8. Between Week 8 and Week 16, the prevalence of oral adverse events

exceeded 15% of the study population, with a higher percentage of events classified as moderate to severe than earlier in the study.

Hypersensitivity-related adverse events generally occurred soon after treatment initiation, and remained mild in intensity.

Figure 1: Time-to-Event distribution of prevalence for oral/pharyngeal adverse event clusters (cumulative safety population)

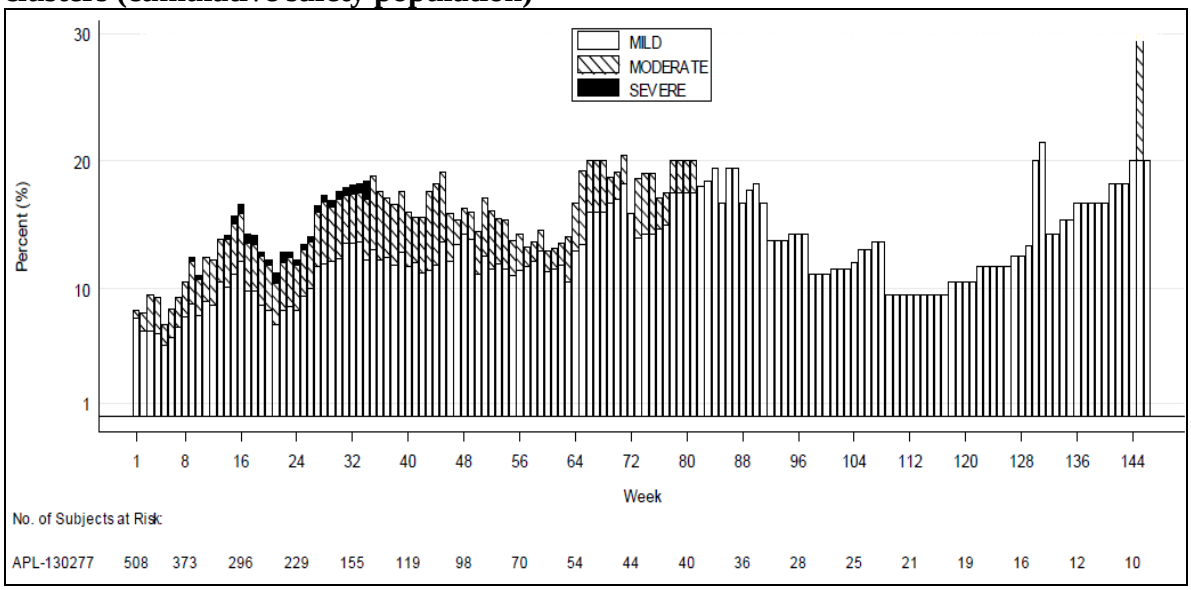
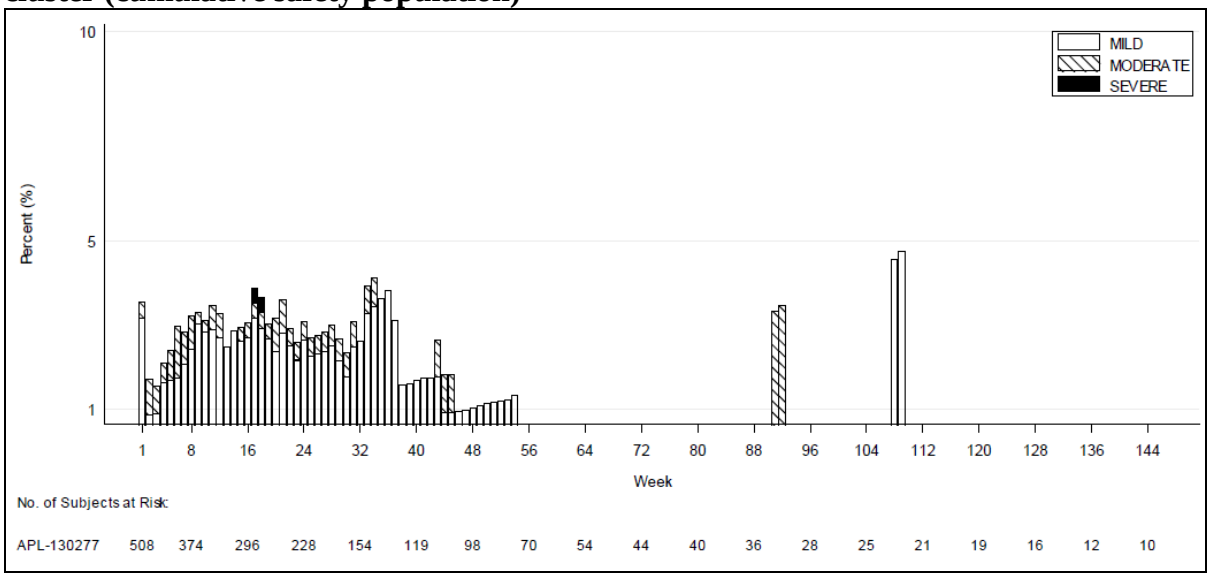


Figure 2: Time-to-Event distribution of prevalence for the hypersensitivity adverse event cluster (cumulative safety population)



Of the 500 oropharyngeal adverse events reported for the combined titration and maintenance phase of Study 300/301, 12% had not resolved by the data cutoff. The clusters with events

most commonly not resolved at cutoff (as a proportion of total events) were alterations in taste, oropharyngeal numbness/changes in sensation, and salivary complaints/oral dryness.

A trend towards a dose-response was observed for some oropharyngeal clusters, but a clear interpretation was precluded by the titration of study medication to tolerance.

Anaphylaxis, angioedema, and hypersensitivity reactions

The applicant and Dr. Bergmann found no cases that fulfilled the criteria for anaphylaxis. Both broad and narrow search criteria were used and identified cases of local oral or pharyngeal swelling that were primarily localized to the mouth and face, without other signs of anaphylaxis. There were few cases associated with systemic hypersensitivity (e.g., urticaria) that were not temporally related to the oral adverse event. None of the events were associated with life-threatening outcomes, and symptoms resolved with discontinuation of Kynmobi. The applicant's expert consultant (David Margolis, MD) came to a similar conclusion in his report.

Consultation by the Division of Dermatology and Dentistry

The review team consulted the Division of Dermatology and Dentistry (DDD) for assistance in interpreting photographs for oropharyngeal adverse events included in the applicant's complete response. Assistance was also requested in evaluating the applicant's expert opinion about oropharyngeal adverse events associated with Kynmobi.

Natalia Chalmers, DDS, PhD, was the primary dental reviewer for this consult. David Kettl, MD, was the team leader, and supervisory concurrence was provided by Kendall Marcus, MD, Division Director.

The dental reviewer agreed that the applicant addressed the issues listed in the complete response letter. Overall, the conclusions of the DDD consultants are similar to those of the applicant. The consultant agreed that oral adverse events were generally were mild to moderate in severity, and the symptoms (swelling and mucosal ulcers) resolved with interruption or discontinuation of Kynmobi. The oropharyngeal adverse events do not appear to be related to systemic hypersensitivity.

Safety conclusion

The applicant has adequately addressed the deficiencies that precluded approval included in the Complete Response letter.

The clinical safety information supports the safety of Kynmobi up to a maximum recommended dose of 30 mg.

A thorough analysis of oropharyngeal adverse events finds that the events were generally mild to moderate in severity, remained localized, and resolved when Kynmobi was withheld or discontinued. There is no evidence linking Kynmobi with more serious or life-threatening

hypersensitivity reactions (e.g., anaphylaxis or serious skin reactions). Prescribers will be prominently warned about the risk for oropharyngeal adverse reactions in the Kynmobi label.

7. Other Relevant Regulatory Issues

Human Factors Validation Study

Ebony Whaley, PharmD, BCPPS, Safety Evaluator, Lolita White, Pharm.D., Team leader, QuynhNhu Nguyen, MS, Associate Director for human factors, and Danielle Harris, Pharm.D., Deputy Director, Division of Medication Error Prevention and Analysis (DMEPA), reviewed the human factor study information in the resubmission.

Deficiencies in the original human factors validation (HFV) study discovered during the original NDA review were sent to the applicant in a Discipline Review letter and in the Complete Response letter. Multiple participants committed use errors and experienced close calls while performing critical tasks.

The applicant conducted a root cause analysis to determine the factors that underlie the errors and close calls. The instructions for use were revised to combine the instruction for the administration of the drug product and instructions for operating the child-resistant packaging in a single document. These changes were evaluated in a supplemental HFV study to demonstrate that the revisions were effective in mitigating the errors and did not introduce new risks. Upon review of the study results, DMEPA found that close calls and errors in both critical and noncritical tests that were similar to those found in the initial study. Most errors occurred during administration of the 35-mg dose. Subjects took the 20-mg and 15-mg film at the same time, or improperly took the 15-mg film followed by the 20-mg film. Some users still had difficulty opening the child-resistant packaging due to problems with dexterity.

DMEPA concluded the applicant addressed the residual risk to the extent feasible. Users had other means to open the child-resistant packaging or could ask a caregiver for assistance. Most study participants knew to store the product away from children. DMEPA recommended revisions to the instructions for use, the proposed labels and the prescribing information, which were sent to the applicant. The applicant can implement these recommendations without additional HFV testing.

DMEPA concluded that no additional mitigation strategies are necessary and that the residual risk is acceptable.

Controlled Substance Staff

The applicant referenced information describing the potential for abuse and dependence for the listed drug (Apokyn) under the 505(b)(2) pathway. CSS concluded that apomorphine does not have abuse potential and should not be controlled under the Controlled Substances Act (CSA).

CSS found reports in the literature of people trying to use apomorphine for abuse. In some of the cases, this appears to be because apomorphine contains ‘morphine’ in the name, and individuals believe it will produce opioid-like effects. Apomorphine is actually a non-specific

dopamine agonist, and many individuals stop using the drug when it does not produce the desired effects.

8. Labeling

Proprietary name

The Division of Medication Error Prevention and Analysis sent a letter to the applicant, dated April 29, 2020, stating the proposed proprietary name, Kynmobi is conditionally acceptable.

Physician labeling

The Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy Programs (DMPP) comments and edits were included in the division's review of the label. Final labeling was agreed upon with the applicant.

Carton and immediate container labels

The Office of Prescription Drug Promotion (OPDP) and the Office of Product Quality (OPQ) reviewed the final revisions to the carton and container labels proposed by the applicant. OPDP and OPQ have no additional edits for the carton and container labels.

Patient labeling

The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) provided labeling edits and recommendations.

11. Conclusions and Recommendations

The efficacy of Kynmobi for the acute treatment of "off" episodes in patients with Parkinson's Disease was established in the first review cycle.

The applicant has adequately addressed the deficiencies that led to the Complete Response letter issued after the first review cycle.

The data support approval of Kynmobi with a maximum recommended single dose of 30 mg, taken up to 5 times a day. (b) (4)

The most common adverse reactions associated with Kynmobi are nausea, somnolence and oropharyngeal adverse reactions.

Postmarketing studies

A postmarketing requirement for a drug-drug interaction study is described in the Clinical Pharmacology section of this review.

Comments to be conveyed to the applicant in the regulatory action letter

None other than the postmarketing requirement.

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/

GERALD D PODSKALNY
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ERIC P BASTINGS
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