CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum

DATE: May 8, 2020

FROM: Martha R. Heimann, Ph.D., CMC Lead, Office of New Drug Products/DNDP I

NDA: 210875

SUBJECT: **Approval** Recommendation for NDA 210875

This memorandum conveys the final Office of Pharmaceutical Quality (OPQ) recommendation for the resubmission of NDA 210875, KYNMOBI (apomorphine) sublingual film.

NDA 210875 was originally submitted on 3/28/2019 under 505(b)(2), and relied, in part, on the Agency's previous finding of safety for the drug/device combination product APOKYN (apomorphine injection)/APOKYN Pen. During the first review cycle, the OPQ review team recommended approval from a product quality perspective.[1] Subsequently, Biopharmaceutics deficiencies were identified due to bridging issues raised by the CDER 505(b)(2) committee. Specifically, the applicant used a foreign drug/device combination product, the APO-go Pen, as a comparator in clinical studies, rather than APOKYN, the US listed drug (LD) and a scientific bridge between APOKYN and the foreign product was required. There were insufficient in vitro and device performance data to establish a bridge between the US and foreign products. Therefore, the OPQ recommendation was changed to Complete Response (CR). [2]

In the CR Letter dated 01/29/2019, the Agency recommended that the applicant submit the final study report for a completed comparative bioavailability (BA) study (CTH-203). In Study CTH-203, the single-dose pharmacokinetics (PK) properties of apomorphine from the sublingual film were compared to both APO-go and APOKYN in Parkinson's disease patients. Thus, the study was considered critical to support scientific bridging to the APOKYN.

The applicant resubmitted the NDA on 11/21/2019 with the final report for Study CTH-203. The Office of Clinical Pharmacology (OCP) review team has reviewed the study and determined that it is acceptable to support reliance on FDA's findings of safety for APOKYN. As the applicant has established a PK bridge, there is no need for in vitro bridging.

The 11/21/2019 resubmission did not provide for any CMC changes and all manufacturing and testing facilities associated with the application are currently acceptable. There are no outstanding issues precluding approval.

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[1] Memorandum from Wendy Wilson-Lee, Ph.D., Branch Chief and Application Technical Lead dated 1/22/1019. http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881e81978

[2] Memorandum from Wendy Wilson-Lee, Ph.D., Branch Chief and Application Technical Lead dated 1/29/1019. http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881ec9c52

Martha Heimann

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	210875
Drug Product Name/ Strength	KYNMOBI™ (apomorphine hydrochloride) Sublingual Film, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg
Route of Administration	Sublingual
Applicant Name	Sunovion Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	DN1
RLD/RS Number	NDA 021264
Proposed Indication	Acute, intermittent treatment of OFF episodes associated with Parkinson's disease (b) (4)
Submission Date	11/21/2019 (Resubmission)
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Executive Summary

The current resubmission contains the Applicant's responses to the Complete Response (CR) Letter dated 01/29/2019, including the final study report for the completed Study CTH-203. Study CTH-203 is a comparative bioavailability (BA) study conducted to examine the single-dose pharmacokinetics (PK) properties of apomorphine from the proposed sublingual film (APL-130277) and 2 different formulations of subcutaneous apomorphine (APO-go and APOKYN®) in PD patients and to provide scientific bridging to the US Listed Drug (LD) APOKYN® subcutaneous injection.

As noted in Biopharmaceutics review (dated 01/25/2019) for the original NDA, the complete study report of Study CTH-203 is critical to establish the PK bridge between the US LD product and the active comparator/EU drug product and is vital to Biopharmaceutics Reviewer's bridging evaluation of the device components of the US and the EU reference products. The formulation of the test product used in Study CTH-203 has the same formulation, same manufacturing process, and API supplier as the to-be-marketed formulation, which warrants no additional formulation bridging.

As concluded by the Office of Clinical Pharmacology (OCP) review team, the sublingual film (highest 30 mg dose) has lower bioavailability (i.e.,17% for

AUC∞ and 12% for Cmax) for apomorphine compared to maximum dose of APOKYN subcutaneous injection. Therefore, it is acceptable for the applicant to rely on FDA's findings of safety for APOKYN.

Recommendation:

NDA 210875 (Resubmission) is recommended for approval, considering the successful bridging of the device components PK-based scientific bridging to the US Listed Drug (LD) APOKYN® and for the device components (US and EU reference products).

Leah Falade

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Ta-Chen Wu

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/s/

MARTHA R HEIMANN
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U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: January 29, 2019

TO: Division of Neurology Drug Products

FROM: Wendy I. Wilson-Lee, Ph.D.
Branch Chief

SUBJECT: Change in approval recommendation for Kynmobi (apomorphine hydrochloride) Sublingual Film

APPLICATION/DRUG: NDA 210875

The Office of Pharmaceutical Quality initially recommended a complete response action for NDA 210875 on December 20, 2018 based on insufficient information provided to qualify the (b) (4) drug product degradant (b) (4) at the proposed No More Than (NMT) (b) (4) mcg/film limit. Based on the new finding that the proposed limit for drug product degradant (b) (4) is qualified for safety, OPQ recommended approval of NDA 210875 for Kynmobi (apomorphine hydrochloride) Sublingual Film on January 22, 2019.

After the January 22, 2019 recommendation revision, the CDER 505(b)(2) committee met to discuss the bridging strategy supporting approval. The outcome of this meeting resulted in a revision of the Biopharmaceutics recommendation to complete response due to the lack of a final report for the clinical pharmacokinetics study essential to establish the bridge between the US listed drug product and the active comparator, European Union drug product used in another critical relative bioavailability study. A new biopharmaceutics review was filed on January 25, 2019 which supersedes the original biopharmaceutics filed on December 20, 2018.

Based on this new finding, OPQ recommends a COMPLETE RESPONSE action for NDA 210875.

Wendy
Wilson- Lee

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BIOPHARMACEUTICS

THIS REVIEW SUPERSEDES THE REVIEW FILED ON 12/20/2018.

Product Background:

NDA: 210875; Fast Track Designation; Priority review requested

Drug Product Name / Strength: KYNMOBI® (apomorphine hydrochloride) (b) (4) Film / 10, 15, 20, 25, and 30 mg

Route of Administration: For sublingual administration

Proposed Indication: Acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4)

Proposed Dosage: 10 mg (b) (4) under the tongue, up to 5 times daily (Start with 10 mg, then (if tolerated) titrate to an effective dose.) Doses of 10 mg to 30 mg are administered as a single film. (b) (4) Up to 5 times daily as needed for management of OFF episodes; Doses should be at least 2 hours apart

Maximum Daily Dose: (b) (4)

Applicant Name: Sunovion Pharmaceuticals Inc.

Primary Reviewer: Gerlie Gieser, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Review Recommendation:

From the Biopharmaceutics perspective, NDA 210875 is **not recommended for APPROVAL at this time,** mainly due to an outstanding deficiency related to the lack of a final report for a clinical PK study essential to establish the bridge between the US Listed Drug product and the active comparator/European (EU) drug product used in another critical relative BA study.

Review Summary:

This 505(b)(2) NDA for KYNMOBI® (apomorphine hydrochloride) (b) (4) film (formerly known as APL-130277) for sublingual administration relies for approval, *in part*, on the nonclinical, clinical safety, and clinical pharmacology information of APOKYN® subcutaneous injection [NDA 21-264].

Dosage Form Nomenclature

The proposed drug product intended for sublingual administration is a film strip consisting of (b) (4) the proposed drug product, from the Biopharmaceutics perspective, it is more appropriate to refer to the proposed drug

product as a "sublingual film" or "film for sublingual administration" (b) (4) .

Dissolution Method and Acceptance Criterion

(b) (4)

Based on the data generated from additional FDA requested studies, the dissolution method and acceptance criterion (as tabulated below) are approved for the routine QC of all five proposed commercial strengths of apomorphine sublingual film at batch release and during stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
5 (paddle over disk)	75 rpm	20mM BIS-TRIS HCl pH 6.4 buffer, 37 ± 0.5°C	500 mL	NLT (b) (4)% (Q) of the label claim dissolved in 10 min

Biowaiver/Bridging to the Proposed To-Be-Marketed Drug Product
All proposed commercial strengths of the to-be-marketed drug product were evaluated in the pivotal clinical trials/studies. Additionally, the proposed to-be-marketed drug product has the same formulation and manufacturing process as those used in the pivotal clinical trials/studies and the registration stability studies. Therefore, bridging data to and a biowaiver request(s) for the proposed commercial drug product are not needed.

505(b)(2) Bridging Strategy to the Listed Drug Product - INCOMPLETE
Overall, the provided *in vivo* PK (and supporting *in vitro*) data would have been sufficient to establish the bridge between the proposed apomorphine sublingual film and the Listed Drug product (APOKYN® for subcutaneous administration), thereby allowing the Applicant of this 505(b)(2) NDA to rely, in part, on the nonclinical and clinical systemic safety and clinical pharmacology information for APOKYN. However, the final clinical study report for one of the essential studies was not submitted thereby precluding the thorough evaluation of the comparative PK data by the Office of Clinical Pharmacology (OCP) Reviewers. Thus, the adequacy of the said in vivo PK study vital to this Biopharmaceutics Reviewer's bridging evaluation of the device components of the US and the EU reference products cannot be concluded by OCP at this time. Note that the efficacy and local safety of the proposed drug product (administered sublingually at an *adjusted* dose in order to match systemic exposures to the subcutaneously administered Listed Drug product) were investigated versus placebo in a pivotal Phase 3 trial(s) conducted by the Applicant. For details, refer to "REVIEWER NOTE" on page 10 of this review.

List of Submissions reviewed:
SDN-1, 3/29/2018, Original NDA
SDN-7, 5/25/2018 [Part I Response to 5/17/2018 Biopharmaceutics Information Request (IR)]
SDN-12, 6/15/2018 (Part II Response to 5/17/2018 Biopharmaceutics IR)
SDN-18, 7/27/2018 (Part I Response to 7/12/2018 Biopharmaceutics IR)
SDN-28, 9/18/2018 (Part II Response to 7/12/2018 Biopharmaceutics IR)
SDN-35, 11/27/2018 (Response to 11/15/2018 Biopharmaceutics IR)
SDN-38, 12/13/2018 (Response to11/29/2018 Biopharmaceutics IR)
SDN-39, 12/19/2018 (Response to 12/17/2018 Biopharmaceutics IR)

Concise Description of Outstanding Issues Remaining:
Adequate bridging of the US Listed Drug and the EU reference drug products (pending final study report for CTH-203 for OCP review)

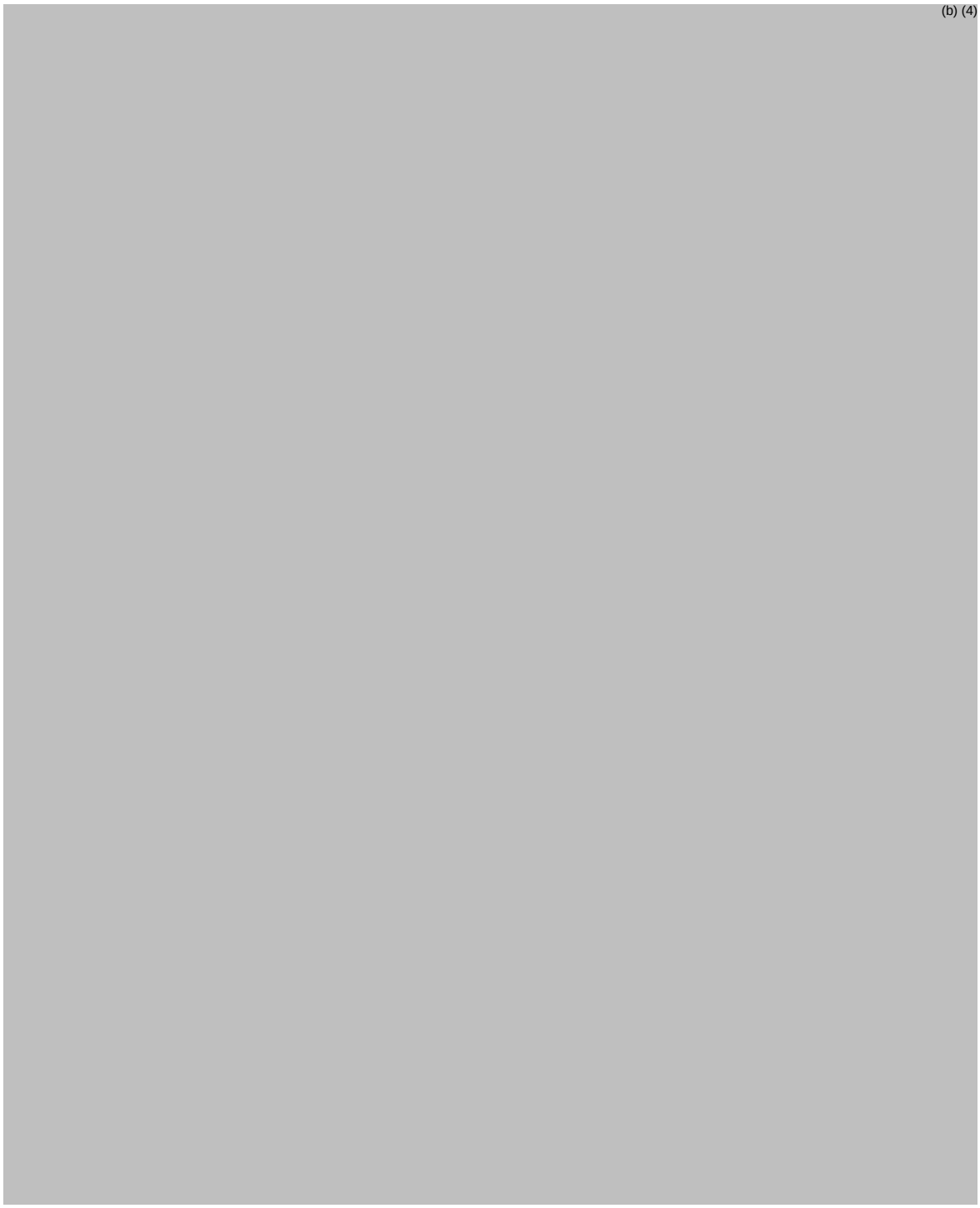
BCS Designation

Reviewer's Assessment: *NOT APPLICABLE*

(b) (4)

(b) (4)

(b) (4)



Disintegration in lieu of Dissolution Testing of the Sublingual film

Reviewer's Assessment: *NOT ACCEPTABLE*

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(b) (4)

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: *DISSOLUTION TESTING RECOMMENDED USING OPTIMIZED METHOD AND ACCEPTANCE CRITERION*

Dissolution Method

Dissolution Method 01512 (as tabulated below) was used during pharmaceutical

(b) (4)

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(b) (4)

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Bridging of Apomorphine Sublingual Film Formulations

Reviewer's Assessment: *NOT NEEDED*

(b) (4)

[redacted]

(b) (4)

[redacted]

REVIEWER NOTE:

The Applicant provided *in vivo* relative bioavailability data comparing the proposed to-be-marketed drug product (Apomorphine Sublingual Film) to two reference products, i.e., the Listed Drug, APOKYN® and the European approved product, Apo-go® subcutaneous (s.c.) injections (CTH-203). The interim PK study report states "The two s.c. formulations were nearly identical to each other with a bioavailability relative to each other of over (b) (4)% when APO-go was compared to APOKYN. Compared to the s.c. regimens, apomorphine sublingual film relative bioavailability was approximately (b) (4)%." Additional relative BA data are available to compare the proposed sublingual film to Apo-go® (CTH-200). Note that during the IND stage, FDA recommended that the PK study report of Study CTH-203 be also included in the NDA to confirm the "sameness" of APOKYN and APO-go. Note that in an internal meeting held on 1/25/2019 among representatives of the Division of Biopharmaceutics, the Office of Clinical Pharmacology (OCP), and the 505(b)(2) Committee, it was concluded that the final clinical study report of PK Study CTH-203 had to be submitted because it is a study essential to supporting the bridge between the US and EU reference products (APOKYN and Apo-go, respectively), and ultimately, the bridge between the US Listed Drug product and the proposed sublingual film product (APOKYN and KYNMOBI, respectively). Note also that previously, the Clinical Pharmacology Reviewer (Dr. Mariam Ahmed) confirmed the adequacy of the comparative *in vivo* PK data generated in relative BA Study CTH-200.

To support the "sameness" of the Listed Drug product to the PK comparator used in an earlier relative BA study CTH-200 (APOKYN® Autopen 10 mg/mL Solution for Injection and Apo-go® PEN 10 mg/mL Solution for Injection, respectively), comparative *in vitro* data (pH, assay, appearance, impurities) were provided for the test and reference injectable solution drug products. This Reviewer confirms that the *drug components* of these two drug-device combination products are comparable in terms of physicochemical properties; see Table 8 of Report SCAR-0878. Additionally, the Applicant pointed out that although APOKYN multi-dose cartridge (but not Apo-go) contains the preservative, benzyl alcohol 5 mg/mL, a version of APOKYN (solution in ampoule) without this preservative was once approved under the same US Prescribing Information; Tables 1 and 2 of the Report show that with the exception of the presence of benzyl alcohol in APOKYN Autopen, the compositions of the two injectable solutions (APOKYN and Apo-go) are the same. However, this Reviewer notes that the

Applicant was not able to provide comparative *in vitro* data with respect to the functional performance characteristics (e.g., activation force, volume dispensed, dispensing time, extended needle length, leakage rate) of the *device components* of these two drug-device combination products. Thus, it was deemed necessary to rely mainly on *in vivo* comparative PK data from Study CTH-203 to establish "sameness" of these two drug-device combination products, i.e., Listed Drug, APOKYN® Auto-pen (multi-dose cartridge, formulation with benzyl alcohol) versus Apo-go PEN (multi-dose cartridge, formulation without benzyl alcohol). Of note, Study CTH-203 was designed to also provide a direct PK comparison of the proposed apomorphine sublingual film versus APOKYN (the Listed Drug product).

For this 505(b)(2) NDA, the Applicant declared reliance, in part, on APOKYN's nonclinical toxicology/PK and clinical PK (metabolism, drug interactions) information. Provided the final PK study report findings of CTH-203 is deemed acceptable/adequate by OCP, in this Reviewer's opinion, it is justified to rely on the FDA's findings of nonclinical and clinical systemic toxicology/safety for subcutaneously administered APOKYN, based on the following information: (1) Based on the (*interim)* comparative clinical PK findings of relative BA Study CTH-203, the systemic bioavailability of apomorphine from the sublingual film is approximately (b) (4)% relative to that following subcutaneous administration of the same dose of the reference product, APOKYN, and the systemic bioavailabilities of APOKYN and Apo-go are similar (b) (4). (2) Thus, as confirmed by Dr. Ahmed, based on the comparative PK findings of CTH-200 and CTH-203, the sublingual administration of the recommended starting dose of 10 mg apomorphine film will provide apomorphine systemic exposures that are similar to those achieved following subcutaneous administration of the recommended starting (2 mg apomorphine) dose of Apo-go or APOKYN. *Refer also to the Medical Review for the evaluation of the findings of Phase 3 clinical trials that evaluated the efficacy and/or (long-term) local safety of the proposed sublingual film, using a starting dose of 10 mg. Refer also to DMEPA's review of the human factors study.* (3) Per the Clinical Pharmacology Reviewer, although the resulting plasma exposures (as $AUC_{0\text{-}inf}$) to the major metabolite, apomorphine sulfate are expected to be substantially higher from the sublingual film as compared to the subcutaneously administered reference products (b) (4) based on the *in vitro* transporter substrate/inhibitor and metabolic inhibition/induction studies conducted by the Applicant, the potential for apomorphine sulfate and apomorphine associated drug interactions are unlikely. Additionally, Dr. Ahmed confirmed that it is appropriate to determine relative bioavailability of the proposed and the reference drug products based on apomorphine (rather than apomorphine sulfate) concentrations because none of the three major metabolites are pharmacologically and toxicologically active. Therefore, such *in vitro* metabolism and drug interaction information provides additional support to the conclusion that the systemic safety of apomorphine sublingual film and APOKYN (b) (4) is expected to be similar.

Biowaiver Request

Reviewer's Assessment: *NOT NEEDED*

A biowaiver request was not submitted (and is no longer deemed necessary) because the Applicant included all five proposed commercial strengths of the final, to-be-marketed apomorphine sublingual film in the clinical efficacy/safety trials.

(b) (4)

List of Deficiencies:

Submission of the final study report for CTH-203 (for OCP review)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: January 22, 2019

TO: Division of Neurology Drug Products

FROM: Wendy I. Wilson-Lee, Ph.D.
Branch Chief

SUBJECT: Change in approval recommendation for Kynmobi (apomorphine hydrochloride) Sublingual Film

APPLICATION/DRUG: NDA 210875

The Office of Pharmaceutical Quality initially recommended a complete response action for NDA 210875 based on insufficient information provided to qualify the (b) (4) drug product degradant (b) (4) at the proposed No More Than (NMT) (b) (4) mcg/film limit. (b) (4) includes a structural alert for mutagenicity. Several rounds of information requests were sent to the applicant requesting additional information to support qualification or reduction of the specification limit to NMT (b) (4) mcg/film to comply with the NMT (b) (4) mcg/day limit for mutagenic impurities. In response to these information requests, the applicant did not revise the specification limit and reiterated the previously submitted justification for the proposed NMT (b) (4) mcg/film limit. Hence, OPQ recommended a complete response action on December 20, 2018.

Since the initial recommendation, OPQ has continued to work with the nonclinical and clinical teams on the qualification of (b) (4) The initial (b) (4) mcg/day limit for (b) (4) was based on the assumption of lifetime exposure (i.e. > 10 years). Additional clarity on the anticipated duration of human use was provided by the clinical team, indicating that the expected use of this product is less than 10 years for most patients. Based on an anticipated duration of human use of < 10 years, the acceptable total daily intake for potentially mutagenic impurities increases to NMT (b) (4) mcg/day (ICH (b) (4) . At the currently proposed limit of NMT (b) (4) mcg/film, the total daily intake would be (b) (4) mcg/day (2 films per dose x 5 doses per day = 10 films per day). This total daily intake is well within the limit established for duration of treatments < 10 years.

Based on the new finding that the proposed limit for drug product degradant (b) (4) is qualified for safety, OPQ recommends approval of NDA 210875 for Kynmobi (apomorphine hydrochloride) Sublingual Film. All deficiencies have been adequately addressed in this review cycle. There are no outstanding issues precluding approval.

Wendy
Wilson- Lee

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Recommendation: COMPLETE RESPONSE

NDA 210875
Review # 01

Drug Name/Dosage Form	Apomorphine Hydrochloride Sublingual Film
Strength	10 mg, 15 mg, 20 mg, 25 mg, 30 mg
Route of Administration	Sublingual
Rx/OTC Dispensed	Rx
Applicant	Sunovion Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	29-MAR-2018	*Amendment*	13-AUG-2018
Amendment	25-MAY-2018	*Amendment*	22-AUG-2018
Amendment	13-JUN-2018	*Amendment*	18-SEP-2018
Amendment	15-JUN-2018	*Amendment*	21-SEP-2018
Amendment	15-JUN-2018	*Amendment*	30-OCT-2018
Amendment	18-JUN-2018	*Amendment*	27-NOV-2018
Amendment	12-JUL-2018	*Amendment*	30-NOV-2018
Amendment	20-JUL-2018	*Amendment*	07-DEC-2018
Amendment	27-JUL-2018	*Amendment*	13-DEC-2018
Amendment	03-AUG-2018	*Amendment*	19-DEC-2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Ben Zhang	Suong Tran	ONDP
Drug Product	Rao Kambhampati	Wendy Wilson-Lee	
Environmental			
Labeling			
Process	Yuesheng Ye	Nallaperumal Chidambaram	OPF
Facility		Ruth Moore	
Biopharmaceutics	Gerlie Geiser	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Apomorphine hydrochloride	Adequate	15-AUG-2018	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110955	Apomorphine Film
NDA	21264	APOKYN (apomorphine) Injection

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends a COMPLETE RESPONSE for NDA 210875 due to inadequate controls for a mutagenic impurity in the drug product.

Draft Complete Response Deficiency

The proposed drug product limit for the orthoquinone degradant (b) (4) *mcg/film) is not acceptable as it results in a daily intake of* (b) (4) *mcg/day for this potentially mutagenic impurity at the maximum recommended dose (2 films per dose X 5 doses per day = 10 films). The data and justification provided in the submission were not adequate to support* (b) (4) *mcg/day intake given the likely chronic administration for this product. As such, provide a revised drug product specification that reflects a control limit for* (b) (4) *that ensures a NMT* (b) (4) *mcg/day intake based on the maximum recommended dose (i.e. 10 films). Revise all relevant sections of the submission to reflect this change. Alternatively, provide additional justification, supported by data, to demonstrate that the proposed* (b) (4) *mcg/day intake of* (b) (4) *is safe.*

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Treatment of acute, intermittent hypomobility "OFF" episodes associated with Parkinson's Disease***
Duration of Treatment	***Chronic***
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	***None***

The Applicant is seeking approval of Apomorphine Sublingual Film as an acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4) The sublingual film dosage form is an alternative dosage form to the listed drug APOKYN (apomorphine) Injection for subcutaneous administration (NDA 21264, approved April 2004). The subcutaneous injection is the only FDA-approved apomorphine product. FDA granted Fast Track designation for the sublingual film dosage form (August 2016). FDA reached agreement with the Applicant regarding the initial pediatric study plan in August 2015 (intent to request full waiver based on disease). OPQ provided advice on the development program as part of the End of Phase

2 Meeting (March 2015; Topics – stability protocol, packaging integrity, excipient control strategy, impurity/degradant control strategy) and via an Advice Letter (April 2016; Topic – determination of product sameness).

The drug product (b) (4) consisting of an active apomorphine HCl (b) (4) The apomorphine hydrochloride drug substance used in the product is manufactured to comply with the current USP monograph under (b) (4) DMF. The sublingual film is a blue, rectangular film with white imprints to distinguish the strength. The bulk master (b) (4)

(b) (4)

B. Quality Assessment Overview

The apomorphine hydrochloride drug substance used in the product is manufactured to comply with the current USP monograph under (b) (4) DMF (b) (4). Batch analysis data for the three registration batches was provided in the NDA. The drug substance specification was provided in the NDA in response to an information request. The DMF has been reviewed and found acceptable. **Based on the stability study data, the DMF holder proposed an (b) (4) retest date for (b) (4) drug substance.**

The applicant developed apomorphine hydrochloride sublingual film (APL-130277), which is a soluble, blue to green (b) (4) film strip designed to deliver apomorphine systemically. (b) (4) strengths of APL-130277 (10, 15, 20, 25, 30 (b) (4) are manufactured. Dosage units are individually packaged into peelable composite foil laminate pouches. Information for the 35 mg strength was included in the NDA to support the registration stability bracketing design but the 35 mg strength is not intended for commercial use. The components and composition for all strengths were adequately described. Adequate information and specifications were provided for non-compendial excipients.

The revised specifications for the drug product are not adequate because the applicant could not (b) (4) limit (b) (4) as proposed by the pharm/tox reviewer. All the analytical methods were adequately described, and validation reports were provided for non-compendial methods. The batch analyses results were provided for seventeen representative batches which showed that the drug product can be manufactured with consistent quality and purity. All three drug related impurities/degradants were identified and adequate justification was provided for (b) (4) the applicant could not (b) (4) as suggested by the pharm/tox reviewer. The USP reference standard is used for the active ingredient and adequate characterization information was provided for the three impurity/degradant standards.

The primary container closure system (foil laminate pouch) was adequately described and a letter of authorization was provided for the cross-reference of the relevant information in the DMF. The secondary container is a child resistant carton. (b) (4)

Adequate CMC information was provided for the placebo film, in which the active ingredient (b) (4) Appropriate tests are included in the specification to ensure the absence of drug substance, appropriate pH, and suitable performance. The primary packaging system proposed is same as the one used for the drug product. Since the placebo is used for the demonstration purposes only, a non-child resistant carton is used as the secondary packaging system. The proposed stability protocol is adequate. The bracketing approach is same as the one followed for drug product. (b) (4)

The drug product manufacturing process includes the following manufacturing steps: (b) (4)

(b) (4)

Following a review of the application and inspectional documents, there are no significant manufacturing deficiencies that prevent approval of this application. All facilities listed are acceptable. A for-cause memo dated November 18, 2018 requested inspection of (b) (4) to follow up on recalls and complaints related to a commercial sublingual film manufactured by the facility. OPQ recommended that the post-approval inspection include coverage for product manufactured under NDA 210875 to ensure that manufacture of the drug product is not adversely impacted by any concerns or findings related to the pending for-cause inspection. (b) (4)

(b) (4)

All proposed commercial strengths of the to-be-marketed drug product were evaluated in the pivotal clinical trials/studies. Additionally, the proposed to-be-marketed drug product has the same formulation and manufacturing process as those used in the pivotal clinical trials/studies and the registration stability studies. Therefore, bridging data to and a biowaiver request(s) for the proposed commercial drug product are not needed.

Overall, the provided in vivo PK (and supporting in vitro) data established the bridge between the proposed apomorphine sublingual film and the Listed Drug product (APOKYN® for subcutaneous administration), thereby allowing the Applicant of this 505(b)(2) NDA to rely, in part, on the nonclinical and clinical systemic safety and clinical pharmacology information for APOKYN. Note that the efficacy and local safety of the proposed drug product (administered sublingually at an adjusted dose in order to match systemic exposures to the subcutaneously administered Listed Drug product) were investigated versus placebo in a pivotal Phase 3 trial(s) conducted by the Applicant.

C. Special Product Quality Labeling Recommendations

Due to the use of sodium metabisulfite in the drug product, a statement regarding potential allergic reactions should be included in the Warnings and Precautions sections of the prescribing information.

D. Final Drug Product Risk Assessment

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation Raw Materials Container Closure Process/Scale/Equipment Site	Medium	End product testing via several direct and indirect measures	Acceptable	
Solid State		Medium	Information submitted to demonstrate manufacturing does not impact solid state	Acceptable	
Content Uniformity		Medium	In-process controls and end product testing	Acceptable	
Microbial Limits		Low		Acceptable	
Dissolution		High	Applicant agreed to implement a suitable dissolution method with appropriate acceptance criterion	Acceptable	
pH		Medium	Buffered formulation, In-process controls and end product testing based on physiologically compatible range	Acceptable	

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Palatability		Medium	(b) (4)	Acceptable	
Disintegration		Medium	Dissolution testing implemented for quality control of the drug product	Acceptable	
Film Integrity		Medium	Formulation components and packaging included to maintain film integrity	Acceptable	Recent FAERS reports for similar products from the applicant include reports of film integrity issues
Particle Size		Low		Acceptable	
Film Dimensions		Medium	In process controls	Acceptable	
Water Content		Low		Acceptable	
Viscosity		Medium	Controlled by formulation components and manufacturing process	Acceptable	

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LABELING
NDA 210875

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Kynmobi™ (apomorphine hydrochloride) sublingual film
Dosage form, route of administration	Yes
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes (10 mg, 15 mg, 20 mg, 25 mg, and 30 mg of apomorphine hydrochloride/film)

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	No
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Yes (appearance and solubility of active ingredient)

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	No but provided at the end of the prescribing information.

Reviewer's Assessment of Package Insert: ***Adequate***

The revised Prescribing Information complies with all regulatory requirements from the CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

Kynmobi 10 mg Trade Foil Pouch:

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Yes
Dosage strength	Yes	Yes
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	No but included on the outer carton	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	No but included on the foil pouch label.
Storage conditions	No but included on the outer carton.	Yes
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	Use instructions were provided	Use instructions were provided

Reviewer's Assessment of Labels: ***Adequate with following modifications:***

1) **Include lot number and expiration date on the trade cartons.**
2) **Under the tradename, increase the prominence of the established name on the foil pouch and outer carton.**

The labels comply with all regulatory requirements from the CMC perspective after the above suggested edits.

List of Deficiencies:

1) ***Include lot number and expiration date on the trade cartons.***

2) ***Under the tradename, increase prominence of the established name on the foil pouches and outer cartons.***

Overall Assessment and Recommendation: Adequate after the above two deficiencies are fulfilled.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 12/6/2018

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 12/6/18

Rao Kambhampati

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Wendy Wilson- Lee

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