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APPLICATION NUMBER:

210875Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	210875
Link to EDR	\\cdsesub1\evsprod\nda210875\0044
Submission Date	11/21/2019
Submission Type	NDA resubmission
Proprietary Name	To be determined
Dosage Form and Strength	Sublingual (SL) film 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg
Proposed Dose/Regimen	The proposed dose range for APL-130277 is 10 mg (b) (4) mg. Dose titration should be initiated with 10 mg dose when patients are in an "OFF" state. Continue dose titration until an effective and tolerable dose is achieved. Do not administer more than 5 doses per day.
Proposed Indication	For the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4) (b) (4) (b) (4)
Applicant	Sunovion Pharmaceuticals, Inc.
OCP Division	Division of Neuropsychiatric Pharmacology
Associated IND	110955
OCP Review Team	Mariam Ahmed Ph.D., Sreedharan Sabarinath Ph.D. and Mehul Mehta, Ph.D.

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1. Executive Summary

This is a resubmission to address the deficiencies outlined in the complete response letter (CRL) to the original NDA 210875 (CRL dated 29 January 2019) for apomorphine sublingual (SL) film (APL-130277). The CRL identified three major sources of deficiencies: human factors, clinical pharmacology and biopharmaceutics, and safety.

To address the clinical pharmacology and biopharmaceutics deficiency identified in the CRL, the division requested the applicant (Sunovion Pharmaceuticals, Inc.) to complete and provide the final report of Study CTH-203 to support the scientific appropriateness of reliance on FDA's finding of nonclinical safety and applicable clinical pharmacology information for the listed drug, APOKYN® (apomorphine hydrochloride injection). In addition, the CRL included additional comments and recommendations which were not approvability issues. These included recommendations to conduct in vitro studies to evaluate the drug-drug interaction (DDI) potential of two major metabolites of apomorphine from the proposed SL product (APL-130277): apomorphine glucuronide and norapomorphine glucuronide.

In this resubmission, the applicant included the complete study report of the relative bioavailability study (CTH-203) and in vitro DDI studies for apomorphine glucuronide. Study CTH-203 was conducted to assess the comparative PK of apomorphine from APL-130277, APOKYN (relied-upon listed drug) and APO-go (European product) in a 3-way crossover design in patients with Parkinson's Disease (PD).

The primary focus of this review is to assess the acceptability of the bridge between APL-130277 and the listed drug. Although the applicant initially proposed [redacted] (b) (4) for APL-130277, the clinical review team is recommending approval of doses [redacted] (b) (4) up to 30 mg [redacted] (b) (4). This review also evaluates the in vitro DDI results for apomorphine glucuronide.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval.

The SL route has lower bioavailability for apomorphine compared to subcutaneous (S.C.) injection. The bioavailability for APL-130277 relative to APOKYN is about 17% for AUC_{inf} and 12% for C_{max}. The doses of APL-130277 were adjusted for the difference in bioavailability of apomorphine for the proposed SL route of administration. The recommended dose range of the proposed SL product APL-130277 is 10-30 mg, while APOKYN's approved dose range is 2-6 mg. Based on Study CTH-203, the exposures of apomorphine from the recommended highest dose of APL-130277 (30 mg) are lower for APL-130277 compared to the maximum dose of APOKYN.

Therefore, it is acceptable for the applicant to rely on FDA's finding of non-clinical safety and clinical pharmacology for APOKYN. The clinical safety and efficacy data for APL-130277 is available from their own clinical development program.

1.2 Post-Marketing Requirements and Commitments

The applicant should submit in vitro studies that evaluate the DDI potential for the major metabolite norapomorphine glucuronide, as listed in the original clinical pharmacology review for NDA 210875 in DARRTS dated 12/29/2018.

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