CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: January 24, 2019

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 210-875 (Kynmobi, apomorphine hydrochloride sublingual film, APL-130277)

NDA 210-875, a 505(b)(2) application, was submitted by Sunovion Pharmaceuticals on March 29, 2018, to request marketing approval for apomorphine hydrochloride sublingual film for the "intermittent 'OFF' episodes associated with Parkinson's disease (b) (4)

NDA 210-875 relies, in part, on findings of safety and effectiveness of a previously approved drug. The listed drug is Apokyn (apomorphine hydrochloride for subcutaneous injection), approved (NDA 21-264) for "the acute, intermittent treatment of hypomobility, 'off' episodes ('end-of-dose wearing off' and unpredictable 'on/off' episodes) associated with advanced Parkinson's disease." Clinical development was conducted under IND 110955.

To support clinical development and an NDA, the sponsor conducted GLP studies to assess the local toxicity of apomorphine (28-day cheek pouch toxicity in hamster) and the toxicity and toxicokinetics of metabolite, apomorphine sulfate (13-week oral toxicity of apomorphine in rat). These (and preliminary dose-ranging studies) were reviewed by Dr. McKinney, who has concluded the nonclinical data support approval of the NDA (Pharmacology/Toxicology Review and Evaluation, NDA 210-875, LuAnn McKinney, DVM, January 24, 2019).

The sponsor provided a scientific bridge to the listed drug in clinical studies, comparing the pharmacokinetics of apomorphine hydrochloride sublingual film to those of Apokyn and APO-g SC injection (approved in Europe). In humans, apomorphine sulfate, apomorphine glucuronide, and norapomorphine glucuronide are major human metabolites (metabolite-to-parent AUC ratios were 9.6, 131, and 10.4, respectively). Plasma AUC values for these major human metabolites were, "4.4, 15.8, and 9.1fold [respectively] greater following SL administration compared to SC…" (Office of Clinical Pharmacology Review, NDA 210875, Mariam Ahmed, PhD, Kevin Krudys, PhD, Sreedharan Sabarinath, PhD, December 28, 2018). Because these metabolites are conjugates, which were not considered of toxicological concern (e.g., not acyl glucuronides), additional nonclinical studies of these metabolites were not required. A local tolerance study was initially recommended, but it not required because the clinical team agreed the local effects of the product could be adequately evaluated in humans.

As noted, the sponsor assessed the toxicity of apomorphine sulfate (following oral administration of apomorphine) and the local tolerance of APL-130277 (sublingual film) in nonclinical studies. In the 28-day study in Sprague Dawley rat (10/sex/group + 9/sex/dose group for toxicokinetic analysis), apomorphine was administered by oral gavage at doses of 0, 3, 10, or 30 mg/kg QD. No drug-related effects were observed. At the high dose, plasma C_{max} and $AUC_{(0\text{-}24\ h)}$ for apomorphine sulfate were 2400-767 ng/mL and 11000-3150 ng*hr/mL, respectively. At the maximum recommended human dose (MRHD: 5 x 35 mg/day, 10 films/day), plasma C_{max} and $AUC_{(0\text{-}24\ hr)}$ for the metabolite were 1220 ng/mL and 13160 ng*hr/mL. In the local tolerance study, APL-130277 was applied to the buccal mucosa (cheek pouch) of Golden Syrian hamsters (8/sex/group) at a dose of 0 or 2.08 mg apomorphine TID for 28 days. No local irritation was detected. These studies did not provide adequate margins (based on metabolite exposure or local APL-130277 concentration) compared to humans; however, neither study was considered essential for clinical development or an NDA.

An additional issue was the specification limit for one impurity, Impurity (b) (4) which was positive for bacterial mutagenicity in an adequate (Q)SAR evaluation. The specification limit would result in a total daily dose of (b) (4) at the MRHD. This is acceptable from a nonclinical standpoint because the anticipated human use for the proposed indication is ≤10 yrs, for which the daily limit for a mutagenic impurity is (b) (4) March 2018).

Recommendation

From a nonclinical standpoint, there is no objection to approval of the NDA.

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/s/

LOIS M FREED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210875
Supporting document/s:	eCTD/SDN 0001
Applicant's letter date:	MAR 29 2018
CDER stamp date:	MAR 29 2018
Product:	APL-130277 Sublingual Apomorphine Thin Film Strip
Indication:	Parkinson's disease
Applicant:	Sunovion Pharmaceuticals, Inc. 84 Waterford Drive Marlborough, MA 01752-7010
Review Division:	Division of Neurology Products
Reviewer:	LuAnn McKinney, DVM, DACVP
Supervisor:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Jack Dan, PharmD

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