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

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210875 are owned by Sunovion Pharmaceuticals, Inc. or are data for which Sunovion Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 210875 that Sunovion Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 210875.

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1 Executive Summary

1.1 Introduction

Sunovion Pharmaceuticals, Inc. submitted this NDA for Kynmobi®, a sublingual film formulation of apomorphine HCl, for the acute, intermittent treatment of "off" episodes in Parkinson's disease patients.

Pursuant to Section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act, Sunovion Pharmaceuticals is relying on the Agency's finding of safety for the listed drug, APOKYN® injectable apomorphine (NDA 21264, approved on APR 20, 2004). The sponsor submitted clinical data to establish a pharmacokinetic bridge to the listed drug.

1.2 Brief Discussion of Nonclinical Findings

In nonclinical studies in rabbit and golden hamster, the sublingual drug product produced no irritation to oral or cheek pouch mucosa. In a 90-day toxicity study in rat, oral administration of apomorphine resulted in circulating levels of the major metabolite, apomorphine sulfate, similar to those seen clinically at the MRHD. No adverse in-life or post mortem findings were reported and there should be little or no toxicologic risk from clinical administration via the sublingual route.

Pyridoxine HCl (b) (4) film and at the MRHD of one 20 mg plus one 15 mg strip, five times daily, the daily dose of pyridoxine would be (b) (4). Although this exceeds the dietary dose of (b) (4) per day and is slightly higher than the (b) (4) daily dose administered for pyridoxine-dependent seizures, the clinical team finds (b) (4) to be acceptable.

In stability studies, three degradant impurities were identified. Two are structurally similar to apomorphine and are not considered to be of concern; the third, a (b) (4) is specified at an acceptable intake based on the advanced age of the patient population.

1.3 Recommendations

1.3.1 Approvability

This New Drug Application is approvable from a nonclinical perspective.

1.3.3 Labeling

Labeling largely reflects that approved for the listed drug; however, the comparisons of nonclinical doses are to the MRHD for subcutaneously administered APOKYN® (20 mg/day). These should be corrected to reflect exposures at the MRHD of the sublingual drug product (b) (4)

Sponsor's table:

APPENDIX 3. APOMORPHINE PHARMACOKINETIC PARAMETERS AND COMPARATIVE BIOAVAILABILITY OF SUBLINGUAL APOMORPHINE (APL-130277) AND SUBCUTANEOUS APOMORPHINE (APOKYN AND APO-GO)

Study CTH-200 in Healthy Subjects (Final Data)

	Sublingual Apomorphine (15 mg APL-130277)				Subcutaneous Apomorphine (2 mg APO-go)				GLSM of Test/Reference (%)	
	C_{max} (ng/mL)	t_{max} (h)	AUC_{∞} (h*ng/mL)	$t_{½}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{∞} (h*ng/mL)	$t_{½}$ (h)	C_{max} [90% CI (%)]	AUC [90% CI (%)]
CTH-200 PK Report	N=19 4.95 (73.2)	N=19 0.85 (0.52-1.05)	N=16 10.4 (68.1)	N=16 1.75 (43.6)	N=19 6.15 (40.7)	N=19 0.38 (0.35-1.02)	N=16 7.87 (20.4)	N=16 0.904 (50.7%)	81.2 (65.9-100.0)	141 (116.2-172.0)

AUC: area under concentration-time curve; CI: confidence interval; C_{max}: maximum concentration; CV: coefficient of variation; GLSM: geometric least squares mean; $t_{½}$: half-life; t_{max}: time of maximum concentration.
Note: Geometric mean (geometric %CV) for all parameters except t_{max}; t_{max} is presented as median (range).

2 Drug Information

2.1 Drug

CAS Registry Number: 41372-20-7

Generic Name: Apomorphine hydrochloride

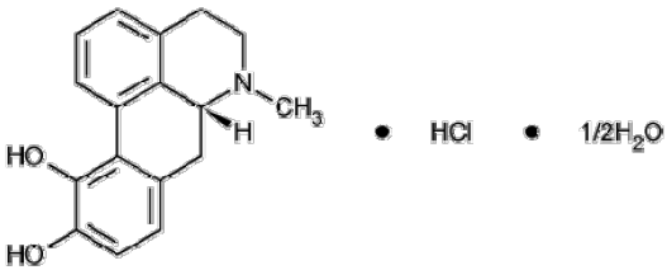
Code Name: APL 130277

Chemical Name: 4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate (salt)

Molecular Formula: C17 H17 NO2 • HCl • ½ H2O (salt)

Molecular Mass: 312.79 (apomorphine hydrochloride hemihydrate)

Structure:
Sponsor's figure:



Pharmacologic Class: Non-ergoline dopamine agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110955
NDA 21264 (Apokyn ®)

Right of Reference to DMF (b) (4), Type II (b) (4)

2.3 Drug Formulation

The drug product (b) (4) dissolving film strip (b) (4) containing apomorphine HCl and (b) (4) pyridoxine HCl/sodium hydroxide. Six strengths of APL-130277 (10, 15, 20, 25, 30 mg), are individually packaged into foil laminate pouches. (b) (4)

Sponsor's table:

Table 3.2.P.1.1-1 Dosage Strength and Film Size

Apomorphine Hydrochloride Loading (mg)	Length (mm)	Width (mm)	Area (mm^2)
10	22	8.8	193.6
15	22	13.2	290.4
25	22	22	484.0
20	22	17.6	387.2
30	22	26.4	580.8

2.4 Comments on Novel Excipients

There are no novel excipients.

Sponsor's table:

Table 3.2.P.2.1-2: Excipients used in APL-130277 Sublingual Thin Film

Material	Reference to Standards	BSE/TSE Free	FDA IIG[1] Listed Max (ODT/ chewable/Oral)	FDA IIG Listed Max. Sublingual Use	Max. Usage Level in Formulation (per Strip)	GRAS Listed
Pyridoxine Hydrochloride	USP	Yes	(b) (4)			Yes
Sodium Metabisulfite	USP	Yes				Yes
Disodium EDTA, (b) (4)	NF	Yes				No
Maltodextrin (b) (4)	USP	Yes				Yes
(b) (4) (-) - Menthol	NF	Yes				Yes
(b) (4) Glyceryl Monostearate	USP	Yes				Yes
Glycerin, (b) (4)	USP/NF	Yes				Yes
Sucralose	USP	Yes				No
(b) (4) Hydroxyethyl Cellulose	USP/NF	Yes				No
Sodium Hydroxide (b) (4)	NF	Yes				Yes
(b) (4) Hydroxypropyl Cellulose, (b) (4)	NF/FCC	Yes				No
FD&C Blue #1 (b) (4) (b) (4)	N/A	Yes				No

[1] Data obtained from CDER database last updated October 24, 2013; *sublingual; tablet

Pyridoxine HCl [redacted]. The MRHD of one 15 mg and one 20 mg strips, to be taken five times daily, results in a daily dose of [redacted] pyridoxine.

Sponsor's table:

Table 2: Levels of Pyridoxine Hydrochloride at Different Dose Strengths

APL-130277 Dose Strength	Pyridoxine HCl Intake (Single Dose)	Maximum Daily Intake (Assumes Five Doses/Day)
10 mg	[redacted]	
15 mg		
20 mg		
25 mg		
30 mg		
35 mg		

2.5 Comments on Impurities/Degradants of Concern

There are three identified degradant impurities in the drug product films. Degradants [redacted] have structural similarity to apomorphine [redacted] In stability studies, the maximum level of Impurity [redacted] was [redacted] per film, after long term (31 months) storage at room temperature. An [redacted] degradant impurity [redacted] is an oxidation product with a structural alert [redacted] for mutagenicity and a proposed acceptance criterion of [redacted]/film.

Sponsor's figure:

The proposed criterion of (b) (4) per film for Impurity (b) (4) results in an acceptable daily intake of (b) (4) from 5 daily single films of 10, 15, 20, or 25 mg. The MRHD of 35 mg consists of one 15 mg plus one 20 mg film resulting in a daily application of 10 films; this yields a daily intake of (b) (4) This exceeds the acceptable daily intake specified for a treatment duration of greater than 10 years'; however, it a clinical judgement that patients in advanced stages of the disease would be unlikely to take the drug for ten or more years. As such, (b) (4) per film is acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

The dosing regimen is sublingual administration for the acute, intermittent treatment of "off" episodes in Parkinson's disease patients, every two hours, not to exceed 5 doses daily. The highest dosage of (b) (4) dose results in a total daily dose of (b) (4) of apomorphine HCl.

2.7 Regulatory Background

The sponsor submitted IND 110995 on June 15, 2014, and a May Proceed letter was issued on August 7, 2014. Fast Track designation was granted on August 25, 2016.

This NDA (210875) was submitted on March 29, 2018. The proprietary name, Kynmobi®, was found to be conditionally acceptable (letter dated June 15, 2018).

3 Studies Submitted

3.1 Studies Reviewed

Oral local irritation studies were submitted and reviewed under the IND (110955). Submitted to the NDA and reviewed were the following:

1) TK of oral dose apomorphine by sublingual administration into male New Zealand white (NZW) rabbits. NPS1637-RPT001: Toxicokinetic report from 11C46Q1G12.
2) Tolerability and toxicokinetic assessment of apomorphine by oral gavage in Rats.
3) Oral gavage toxicity and toxicokinetic study of a metabolite of apomorphine (apomorphine sulfate) in rats.

3.2 Studies Not Reviewed: NA

3.3 Previous Reviews Referenced

IND 110955: Pharmacology/Toxicology review of local irritation studies in hamster cheek pouches. February 3, 2017. LuAnn McKinney, DVM, DACVP.

4 Pharmacology

4.1 Primary Pharmacology

Per the APOKYN® label:
"[Apomorphine HCl] is a non-ergoline dopamine agonist with high *in vitro* binding affinity for the dopamine D_4 receptor, and moderate affinity for the dopamine D_2, D_3, and D_5, and adrenergic α_1D, α_2B, α_2C receptors. The precise mechanism of action of APOKYN as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D_2-type receptors within the caudate-putamen in the brain."

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

When administered sublingually, apomorphine that is not absorbed through the oral mucosa is presumed to be swallowed. Based on published literature (Vietri M, et al., Xenobiotica, 32(7):587-594, 2002) the sponsor reported that orally administered apomorphine undergoes rapid sulfation in the duodenum and in the liver resulting in high circulating levels of the major metabolite apomorphine sulfate.

The sponsor reported that exposure levels of apomorphine sulfate were higher in healthy volunteers and PD patients after sublingual administration than after subcutaneous administration of apomorphine. Although the bioavailability of apomorphine is reduced when administered by the sublingual route (15% relative to the subcutaneous route), exposure (AUC) to the metabolite, apomorphine sulfate, was

approximately 4.35-fold higher following a sublingual dose of 15 mg compared to a subcutaneous dose of 2 mg (1550 versus 356 h*ng/mL).

6 General Toxicology

6.1 Single-Dose Toxicity

11C46Q1G12: Dosing of Apomorphine by Sublingual Administration into Male New Zealand White (NZW) Rabbits and Collection of Blood Samples for Analysis

Anesthetized male NZW rabbits (8/group) were administered sublingual (b) (4) films of 1.19 mg apomorphine, with either meglumine or with pyridoxine (b) (4), followed immediately by 500 µL of deionized water. On Study Day 1, animals were administered one strip and sampled for TK analysis (0, 10, 20, 30, 40 minutes and 1,2, and 4 hours post dose). On Study Day 2, three strips were administered at 0, 2, and 4 hours, after which the animals were necropsied and examined for gross and/or microscopic evidence of local irritation.

Local irritation assessment:
No macroscopic or microscopic effects on the sublingual tissues were reported.

Toxicokinetics:
The (b) (4) (pyridoxine or meglumine) had little effect on systemic exposures to apomorphine.

Sponsor's table:

Table 3-2. Key Mean (SD) TK Parameters for Apomorphine Following Sublingual Administration of 1.19 mg Apomorphine HCl to Male NZW Rabbits

Group	pH Modifier	Tmax (min)[a]	Cmax (ng/mL)	AUClast (min·ng/mL)
1	Meglumine	10 (10-20)	107 (39.4)	4560 (2110)
2	Pyridoxine	10 (10-20)	100 (24.9)	5340 (1490)

a: Tmax summarized as median (range).
N = 8/group. Group 2 results include corrective action to swap samples for M6449 at 60 and 120 minutes postdose due to suspected error during sample collection and/or analysis; mean (SD) for Group 2 AUClast with data as received was 5440 (1550) min·ng/mL.

6.2 Repeat-Dose Toxicity

6.2.1

Study title: **A tolerability and toxicokinetic assessment of apomorphine by oral gavage in rats**

Study no.:	277-802
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	JUL 10, 2017
GLP compliance:	No
QA statement:	No
Drug/ lot #/ % purity:	Apomorphine/IR00012/85.5% (chloride salt form)

Key Study Findings

- The NOEL was the HD in M and F.
- Apomorphine sulfate levels greatly exceeded parent apomorphine levels.
- Apomorphine exposures increased with dose in a slightly greater than proportional manner. The $AUC_{(0.25\text{-}6h)}$ was approximately 1.5- to 3-fold higher in males than in females; C_{max}: (HDM) 38.3 and (HDF) 43.9 ng/mL; T_{max} was approximately 0.25 hr post-dose
- Apomorphine sulfate exposures increased with dose in a greater than proportional manner and the T_{max} ranged from 0.5 - 6 hr post-dose. The $AUC_{(0.25\text{-}6h)}$, was approximately 4.5 to 5-fold higher in males than in females and C_{max} was 3-fold higher in HDM than in HDF.

Methods

Doses:	0, 3, 10, or 30 mg/kg/day
Frequency of dosing:	Once daily for three days
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	50 mM citrate buffer in DIO water
Species/Strain:	CrL:CD(SD) rat
Number/Sex/Group:	Main study: 3/sex/group; TK: 6/sex/group
Age:	6 weeks
Weight:	M: 175-226g; F: 150-195g
Satellite groups:	NA
Unique study design:	In-life observations were limited to body weight, food consumption, and clinical signs. All animals were euthanized and discarded on Study Day 2.

Observations and Results

Mortality: None

Clinical Signs: No test article effects were reported.

Body Weights: No test article effects were reported.

Feed Consumption: No test article effects were reported.

Histopathology: NA

All animals were euthanized on Study Day 2 and tissues were discarded.

Toxicokinetics:
Exposure to apomorphine sulfate ($AUC_{(0.25\text{-}6h)}$) was 14- to 20-fold (M) and 5- to 10-fold (F) greater that of apomorphine.

Apomorphine:

- Exposure ($AUC_{(0..25\text{-}6h)}$ and $C_{max)}$ was similar-to or slightly greater-than dose-proportional. A 10-fold increase in dose resulted in 16-fold (M) and 9-fold (F) increases in $AUC_{(0.25\text{-}6h)}$ and 10-fold (M) and 9-fold (F) increases in C_{max}.
- $AUC_{(0..25\text{-}6h)}$, was 1.5-fold (LD), 2.3-fold (MD), and 2.7-fold (HD) higher in M than F.
- T_{max} was 5 minutes post-dose, except for HDM, in which the T_{max} was at 2 hours post-dose

Apomorphine Sulfate:

- Exposure ($AUC_{(0.25\text{-}6h)}$ and C_{max}) was greater than dose-proportional. A 10-fold increase in dose (3 to 30 mg/kg/day apomorphine) resulted in 17-fold (M) and 15-fold (F) increases in $AUC_{(0..25\text{-}6h)}$ and 21-fold(M) and 27-fold (F) increases in C_{max}
- $AUC_{(0..25\text{-}6h)}$ was 4.5-5.1 fold higher in M than in F.
- T_{max} ranged from 0.5 to 6 hours post-dose in M and F.

Sponsor's table: Apomorphine

Summary of Toxicokinetic Parameters

Dose	AUC0.5-6 hr (ng•h/mL)	Cmax (ng/mL)	Tmax (hr)
	Day 2	Day 2	Day 2
Males			
3 mg/kg/day	5.70	3.67	0.25
10 mg/kg/day	18.7	5.83	0.5
30 mg/kg/day	91.4	38.3	2
Females			
3 mg/kg/day	3.72	4.75	0.25
10 mg/kg/day	7.96	3.42	0.25
30 mg/kg/day	33.5	43.9	0.25

Apomorphine Sulfate: Sponsor's table

Summary of Toxicokinetic Parameters

Dose	AUC0.5-6 hr (ng•h/mL)	Cmax (ng/mL)	Tmax (hr)
	Day 2	Day 2	Day 2
Males			
3 mg/kg/day	79.6	18.2	1
10 mg/kg/day	376	97.8	4
30 mg/kg/day	1370	389	6
Females			
3 mg/kg/day	17.5	4.94	6
10 mg/kg/day	78.7	24.3	0.5
30 mg/kg/day	269	131	0.5

6.2.2

Study title: A 13-week oral gavage toxicity and toxicokinetic study of a metabolite of apomorphine (apomorphine sulfate) in rats.

Study no.: 277-800
Study report location: eCTD: 4.2.3.4
Conducting laboratory and location: (b) (4)
Date of study initiation: JUL 27, 2017
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Apomorphine HCl, (b) (4) /IR00012/100.5%

Key Study Findings:

The NOEL was the HD in M and F.

- Study Day 91: Apomorphine sulfate
  - $AUC_{(0\text{-}24hr)}$ - M: 11000 and F: 3150 ng•h/mL
  - C_{max} - M: 2400 and F: 767 ng/mL
  - T_{max} - M: 0.5- 1 hr; F: 0.5 hr
- Study Day 91: Apomorphine
  - $AUC_{(0\text{-}24hr)}$ - M: 84.2 and F: 83.8 ng•h/mL
  - C_{max} - M: 13.1 and F: 14.3 ng/mL Day 91
  - T_{max} - M and F: 0.25-0.5 hr

Methods

Doses:	0, 3, 10, 30 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Citrate buffer monohydrate (pH 3.5)
Species/Strain:	Crl:CD(SD) rat
Number/Sex/Group:	10/sex
Age:	7 weeks
Weight:	170-272 g.
Satellite groups:	TK: 3/sex C; 9/sex dosed
Unique study design:	Rats were dosed with parent in order to assess toxicity of the major metabolite.
Deviation from study protocol:	None.

Dose selection: The HD was chosen to target the likely clinical apomorphine sulfate levels after administration of the maximum recommended human dose.

Observations and Results

Mortality:
Two moribund LDF were euthanized subsequent to dosing (gavage) error.

Clinical Signs:
There were no reported test article effects on clinical signs, body weights, food consumption, ophthalmoscopic examination, clinical chemistry values, hematology or coagulation values, urinalysis, organ weights, or macroscopic pathology.

Histopathology
Signed, dated pathology report: Yes
Adequate Battery: Yes (Standard battery)
Peer Review: Yes (Contracted to an outside CRO)
Histological Findings:
No test article histomorphologic effects were reported.

Toxicokinetics:
Study Day 1: 0.25, 0.5, 1, 2, 6 hours post-dose; Study Days 31 and 91: 0.5, 1, 2, 6, 12, and 24 hours post-dose

Apomorphine sulfate:

- Exposure to apomorphine sulfate increased with dose in a greater than dose-proportional manner. A 10-fold increase in apomorphine dose from 3 to 30 mg/kg/day resulted in increase of 11- to 29-fold in AUC and 15- to 45-fold in C_{max} in both M and F.
- $AUC_{(0\text{-}6h)}$ was 2- to 8-fold higher in M than F.
- T_{max} ranged from 0.5 to 4 hours in M and was generally 0.5 hours in F.
- Apomorphine sulfate accumulated over time: from Study Day 1, $AUC_{(0\text{-}6h)}$, increased 2- to 3-fold on Study Day 31 and was 2- to 6-fold higher on Study Day

91. AUC (0-24h) was not reported on Study Day 1 but increased 2- to 3-fold from Study Day 31 to Study Day 91.

Sponsor's table:

Summary of Apomorphine Sulfate Toxicokinetic Parameters

Dose (mg/kg/day)	AUC0-6 hr (ng•h/mL)			AUC0-24 hr (ng•h/mL)			Cmax (ng/mL)			Tmax (h)		
	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91
Males												
3	65.5	165	250	N/A	374	897	17.4	37.0	77.3	4	6	1
10	303	701	1120	N/A	1460	2130	67.0	136	302	4	0.5	0.5
30	1180	3130	6640	N/A	6400	11,000	267	586	2400	4	0.5	1
Females												
3	31.2	48.1	47.0	N/A	105	109	8.07	16.0	17.1	0.5	0.5	0.5
10	97.2	172	365	N/A	358	877	36.3	59.7	113	0.25	0.5	0.5
30	354	831	1720	N/A	1600	3150	125	457	767	0.5	0.5	0.5

N/A = not applicable

Apomorphine:

- Exposure generally increased with dose in a variably dose-proportional manner. A 10-fold increase in apomorphine dose resulted in 10- to 17-fold increases in AUC (excluding Day 91 for LDM) and 4- to 39-fold increases in C_{max} for M and F.
- There was no apparent accumulation in either M or F
- T_{max} was generally 0.25 hours on Study Day 1 and 0.5 hours on Study Days 31 and 91 in both M and F.

Sponsor's table:

Summary of Apomorphine Toxicokinetic Parameters

Dose (mg/kg/day)	AUC0-6 hr (ng•h/mL)			AUC0-24 hr (ng•h/mL)			Cmax (ng/mL)			Tmax (h)		
	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91	Day 1	Day 31	Day 91
Males												
3	4.90	5.81	5.54	N/A	8.02	91.9	4.94	2.31	9.50	0.25	0.5	12
10	12.6	14.9	15.8	N/A	23.0	25.3	4.28	3.97	5.19	0.25	0.5	0.5
30	46.5	44.4	51.0	N/A	76.4	84.2	34.8	11.2	13.1	0.5	0.5	0.5
Females												
3	3.74	5.34	4.03	N/A	8.54	7.28	2.71	3.96	1.58	0.5	0.5	0.5
10	21.1	11.4	13.7	N/A	20.7	29.5	46.4	7.73	5.39	0.25	0.5	0.5
30	61.7	47.3	47.4	N/A	84.8	83.8	106	15.9	14.3	0.25	0.5	0.5

N/A = not applicable

Sponsor's tables: Homogeneity

Results of Homogeneity Analyses

	Group 2 (0.3 mg/mL)	Group 4 (3 mg/mL)
Homogeneity Assessment of the 14 Aug 2017 Formulations		
Mean Concentration (mg/mL)	0.318	3.17
RSD (%)	0.17	1.1
Mean % of Target	106	106
Resuspension Homogeneity Assessment of the 14 Aug 2017 Formulations		
Mean Concentration (mg/mL)	0.311	3.11
RSD (%)	0.71	0.20
Mean % of Target	104	104

Results of Stability Analyses

	Mean Concentration, mg/mL (% of Time Zero)	
	Group 2 (0.3 mg/mL)	Group 4 (3 mg/mL)
10-Day Refrigerated (2°C to 8°C) Storage	98.0	98.0

10 Special Toxicology Studies

Pharmacology/Toxicology review of local irritation studies in hamster cheek pouches. Reviewed for IND 110955; FEB 3, 2017 by LuAnn McKinney, DVM, DACVP.

> "The sponsor submitted 2 pilot studies and one 28-day pivotal study of the local tissue irritating effects of the clinical drug product on cheek pouch epithelium. All studies were conducted in Golden Syrian hamsters."
>
> "In the pivotal local irritation study, 0 or 2.08 mg apomorphine (in a 5.5 x 7.5 mm piece of the clinical film) was applied three times daily to the right cheek pouch of hamsters (8/sex/group) for 28 days."
>
> "There were neither gross nor histologic changes observed in either the control or test-article exposed cheek pouches."
>
> "The dose tested was an MTD and a NOAEL for local irritation. Increased activity, decreased food consumption, and mild to moderate weigh loss were noted in M and F from Days 1 to 15, with lesser effects through Day 28. By Day 28, dosed M lost an average of 2% (≤5%) of starting body weight and dosed F had lost an average of 3% (≤8%) of starting body weight."

11 Integrated Summary and Safety Evaluation

APL 30277/KYNMOBI® is a sublingual film formulation of apomorphine HCl developed for the acute, intermittent treatment of "off" episodes in Parkinson's disease patients.

Submitted under Section 505(b)(2), of the CFR 314.50, this NDA relies the findings of safety and efficacy for the listed drug, APOKYN® injectable apomorphine (NDA 21264 approved on April 20, 2004). In clinical trials submitted to this NDA, the sponsor established a pharmacokinetic bridge to APOKYN®.

The drug product (b) (4) consisting (b) (4) of pyridoxine HCl and flavorings and (b) (4) apomorphine HCl (b) (4) (b) (4) By varying the size of the film, the drug is available in (b) (4) dose strengths (10, 15, 20, and 25 mg); (b) (4) The films are to be taken to effect but not more than 5 times daily.

There are no novel excipients; however, the maximum dose of (b) (4) apomorphine ((b) (4) 5 times daily) results in a daily dose of (b) (4) pyridoxine. This is greater than the recommended dietary dose of (b) (4) per day or the dose of (b) (4) for Vitamin B6 Dependency Syndrome and is slightly higher than the (b) (4) daily dose administered for pyridoxine-dependent seizures. Although not inactive, pyridoxine is listed as GRAS, is a common ingredient in oral vitamin supplements, and the clinical review team find the amount of pyridoxine at the maximal daily dose to be acceptable (See the Clinical Team Leader Review of this NDA).

In stability testing, three degradant impurities of apomorphine were identified. Of the three impurities, (b) (4) have sufficient structural similarity to apomorphine (a (b) (4)) to be of no concern.

Degradant impurity (b) (4) is an (b) (4) product that contains a mutagenic alerting structure (b) (4) ave shown that a similar (b) (4) product of apomorphine is mutagenic in *S. typhimurium* and *E. coli*.

At the MRHD of 10 films a day, the dose of impurity (b) (4) and this exceeds the allowable limit in *ICH M7(R1)* of (b) (4) for potential Class 3 substance impurities that are administered for longer than 10 years.

However, the maximum dose of (b) (4) would be needed by Parkinson's disease patients in the advanced stages of the disease and it is unlikely that this elderly patient population would be taking that dose level for more than 10 years. The *ICH M7 (R1)* recommended daily intake of individual mutagenic impurities for a duration of 1-to-10 years is (b) (4) and the daily intake of (b) (4) at the MRHD is well below that limit.

In local irritation studies, the drug product films were placed three times daily, unilaterally, in hamsters' cheek pouches. No macroscopic or microscopic changes were seen in the exposed mucosa and systemic changes were attributed to the pharmacologic activity of apomorphine. In a sublingual TK study in rabbit, no gross or microscopic changes were noted in the oral mucosa.

Oral administration of apomorphine to humans results in the major metabolite, apomorphine sulfate. In the pivotal 90-day study, apomorphine was administered to SD rats by oral gavage. The sponsor reported no in-life or post mortem effects at any dose level and, at the HD of 30 mg/kg, circulating apomorphine sulfate levels were similar to those seen clinically at the MRHD of 5 daily doses of 35 mg. The absence of observations indicates that there is little or no toxicologic risk from similar exposures to apomorphine sulfate that would result from the clinical sublingual route of administration.

Apomorphine sulfate exposures					
Species	Dose	C_{max} ng/mL	C_{max} Margin To MRHD	AUC ng*h/mL	Margin of AUC to MRHD
Rat HD	30 mg/kg	M:2400 F:767	2.0 0.63	M:11000 F:3150	0.84 0.24
Human MRHD	175 mg/day	1220	1.0	13160	1.0
Human Single HD	35 mg	872		3110	

Evaluation:
The sponsor relies on the findings of safety and efficacy of APOKYN®. This listed drug is administered by subcutaneous injection and the metabolic profile of apomorphine is markedly different when administered orally. In nonclinical studies, the sublingual drug product produced no irritation to oral mucosa and the major metabolite resulting from oral administration resulted in no adverse effects. The proposed route of administration, dose, and duration of therapy are supported by the nonclinical data.

Recommendation:
From a nonclinical perspective, this application is approvable.

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/s/

LUANN MCKINNEY
01/24/2019 12:00:57 PM

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