APL-130277

CTH-203

A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

IND No. 110,955

Version 2.00

10 May 2017

Incorporates Amendment 1.00

SUNOVION PHARMACEUTICALS INC.

84 Waterford Drive
Marlborough, MA 01752, USA
+1 (508) 481-6700

RESTRICTED DISTRIBUTION OF PROTOCOLS

This document contains information confidential and/or of proprietary interest to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. (including their predecessors, subsidiaries or affiliates). The information cannot be disclosed to any third party or used for any purpose other than the purpose for which it is being submitted without the prior written consent of the appropriate Sumitomo Dainippon Pharma company.

This information is being provided to you for the purpose of conducting a clinical study for Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. You may disclose the contents of this protocol to the study personnel under your supervision and to your Institutional Review Board or Independent Ethics Committee for the above purpose. You may not disclose the contents of this protocol to any other parties, unless such disclosure is required by government regulations or laws, without the prior written permission of Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc.

Any data gathered during the conduct of this protocol and supplemental information (eg, a protocol amendment) that may be added to this document is also proprietary to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc., and should be handled consistently with that stated above.

1. EMERGENCY CONTACT INFORMATION

Role in Study	Name	Contact Information
Responsible Physician		
Medical Monitor		
SAE Reporting		

2. INVESTIGATOR APPROVAL STATEMENT

I have read the protocol, CTH-203, Version 2.00, "A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)," and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB/REB/IEC approval.

Principal Investigator

Printed Name: _____

Signature: _____

Date: _____

PROTOCOL

A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Protocol: 10 May 2017

Version 2.00

3. PROTOCOL SYNOPSIS

TITLE	A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)
STUDY PHASE	Phase 2
OBJECTIVES	Primary Objective • To evaluate the pharmacokinetics (PK) and comparative bioavailability of a single dose of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD) complicated by motor fluctuations ("OFF" Episodes). Secondary Objectives • To evaluate the safety and tolerability of the study drugs.
NUMBER OF SUBJECTS	The study plan will require approximately 12 subjects to complete the Three-Way Crossover phase.
PATIENT POPULATION	**Inclusion Criteria** Patients who meet each of the following criteria will be eligible for participation in the study: 1. Male or female ≥ 18 years of age. 2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion). 3. Clinically meaningful response to Levodopa (L-Dopa) with well-defined "OFF" episodes, as determined by the Investigator. 4. Receiving a stable dose of APOKYN® of ≤ 5 mg per dose for at least 4 weeks before the Screening Visit. 5. Receiving stable doses of L-Dopa/carbidopa (immediate or sustained release) administered at least 4 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the Screening Visit. Adjunctive PD medication regimens must be maintained at a stable dose for at least 4 weeks prior to the Screening Visit with the exception that MAO-B inhibitors must be maintained at a stable level for at least 8 weeks prior to the Screening Visit. 6. No planned medication change(s) or surgical intervention anticipated during the course of study. 7. Patients must experience a well-defined "OFF" episode in the morning if they do not take their morning PD medications on schedule, and must be willing to delay morning doses on the 3 study dosing days. 8. Stage III or less on the modified Hoehn and Yahr scale in the "ON" state. 9. Mini–Mental State Examination (MMSE) score > 23. 10. If female and of childbearing potential, must agree to use one of the

	following methods of birth control: • Oral contraceptive; • Contraceptive patch; • Barrier (diaphragm, sponge or condom) plus spermicidal preparations; • Intrauterine contraceptive system; • Levonorgestrel implant; • Medroxyprogesterone acetate contraceptive injection; • Complete abstinence from sexual intercourse; • Hormonal vaginal contraceptive ring; or • Surgical sterilization or partner sterile (must have documented proof). 11. Male patients must be either surgically sterile, agree to be sexually abstinent or use a barrier method of birth control (eg, condom), or maintain a monogamous relationship with a person who is not of child-bearing potential from first study drug administration until 30 days after final drug administration. 12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study. 13. Able to understand the consent form, and to provide written informed consent.
	Exclusion Criteria Patients will be excluded from participation in the study for any of the following reasons: 1. Atypical or secondary parkinsonism. 2. Previous treatment with any of the following: continuous subcutaneous (s.c.) apomorphine infusion; or Duodopa/Duopa. 3. Contraindications to APO-go® or APOKYN® or hypersensitivity to apomorphine hydrochloride or any macrolide antibiotic or any of the ingredients of APO-go® or APOKYN® (notably sodium metabisulfite). 4. Female who is pregnant or lactating. 5. Participation in a clinical trial within 30 days prior to the Screening Visit. 6. Receipt of any investigational (ie, unapproved) medication within 30 days prior to the Screening Visit. 7. Any selective 5HT3 antagonists (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (excluding quetiapine and clozapine) or dopamine depleting agents within 30 days prior to the Screening Visit. 8. Drug or alcohol dependency in the past 12 months. 9. History of malignant melanoma. 10. Clinically significant medical, surgical, or laboratory abnormality in the

opinion of the Investigator.

11. Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis, or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.
12. History of clinically significant hallucinations during the past 6 months.
13. History of clinically significant impulse control disorder(s).
14. Dementia that precludes providing informed consent or would interfere with participation in the study.
15. Current suicidal ideation within one year prior to the Screening Visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 5 years.
16. Donation of blood plasma in the 30 days prior to first dosing.
17. Cankers or mouth sores within 30 days prior to the Screening Visit, or other clinically significant oral pathology in the opinion of the Investigator. The Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling a patient into the study.

STUDY DESIGN

This multi-center study will aim to evaluate the pharmacokinetics (PK) and comparative bioavailability of a single dose of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD). The dose of APOKYN® (≤ 5 mg) will be based on the subjects' current prescribed dose.

The study is designed as an open-label, randomized, three-way crossover. Subjects will receive all three treatment arms with a minimum 1-day wash-out between each visit (excluding the screening visit) and will be randomly assigned to one of the following sequences:

	Period 1	**Period 2**	**Period 3**
Sequence 1	APL-130277	APOKYN®	APO-go®
Sequence 2	APL-130277	APO-go®	APOKYN®
Sequence 3	APOKYN®	APL-130277	APO-go®
Sequence 4	APOKYN®	APO-go®	APL-130277
Sequence 5	APO-go®	APL-130277	APOKYN®
Sequence 6	APO-go®	APOKYN®	APL-130277

Treatment Arms:

1. APL-130277 sublingual thin film
2. Subcutaneous APO-go®
3. Subcutaneous APOKYN®

Study Procedures

Screening Visit

Before any study procedures are performed on any person, informed consent

<table>
<tr><td></td><td>must be obtained. Subjects, who have provided full consent to participate, will arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Their normally scheduled second dose of L-Dopa (without adjunctive PD medication) will be administered in the clinic following confirmation of an “OFF” episode by the Investigator, to ensure that they experience an “ON” response. Eligibility criteria will be assessed by the Investigator. Subjects, who are considered eligible, will be scheduled for the Period 1 Dosing Visit.
Wash-Out Interval
One (1) day before each Period Visit, at a minimum, subjects will be required discontinue subcutaneous APOKYN®; this is referred to as the wash-out interval. L-Dopa and any other adjunctive PD medication will be permitted during this time.
Three-Way Open-Label Randomized Crossover (Period 1, Period 2, Period 3)
Subjects will be asked to return to the clinic the morning of Period 1 (P1) after their usual morning dose of PD medications; but before taking their next dose of medication and will be randomized to one of the 6 treatment sequences.
Subjects will be required to wait to take their normally scheduled second dose of PD medications until after confirmation by the Investigator that the subject is in the “OFF” state and will be dosed according to the randomized treatment sequence with either APL-130277, APO-go® or APOKYN®. All PD medications should be held until 60 minutes after dosing.
Following the same procedures described above, subjects will return to clinic within 3-5 days after Period 1 and will be dosed for Period 2 with one of the other two treatments. Subjects will return to clinic within 3-5 days after Period 2 and will be dosed for Period 3 with the third and last treatment.
All assessments will be performed at each visit according to the Schedule of Events (Table 1).</td></tr>
<tr><td>DOSING ALGORITHM</td><td>APL-130277 and APO-go® dosing in the Three-Way Crossover will be based on the subjects’ current prescribed dose of APOKYN®.
<table>
<tr><th>APOKYN®
Current Prescribed Dose</th><th>APO-go®
Study Dose</th><th>APL-130277
Study Dose*</th></tr>
<tr><td>2 mg</td><td>2 mg</td><td>15 mg</td></tr>
<tr><td>3 mg</td><td>3 mg</td><td>20 mg</td></tr>
<tr><td>4 mg</td><td>4 mg</td><td>25 mg</td></tr>
<tr><td>5 mg</td><td>5 mg</td><td>30 mg</td></tr>
</table>
*These are approximate equivalent doses based on PK data on file.</td></tr>
<tr><td>INVESTIGATIONAL PRODUCT</td><td>APL-130277 sublingual thin film</td></tr>
<tr><td>REFERENCE PRODUCT</td><td>Subcutaneous APO-go®
Subcutaneous APOKYN®</td></tr>
</table>

CONCOMITANT AND CO-ANALGESIC TREATMENT	All subjects: stable doses of a L-Dopa formulation and other stable adjunctive PD medications. If a subject is presently using an anti-emetic they can continue with this treatment at the prescribed dose, otherwise use of an anti-emetic will not be permitted.
PROHIBITED TREATMENT	• Treatment with any form of apomorphine other than study medication(s). • Any selective $5HT_3$ antagonist (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron). • Dopamine antagonists (excluding quetiapine or clozapine) or depleting drugs. • Deep brain stimulation or other neurosurgical PD treatment, continuous s.c. apomorphine infusion or Duodopa/Duopa. • Use of an anti-emetic is not permitted. In cases where a subject is presently using an anti-emetic they will be allowed to continue with this treatment at the prescribed dose.
STUDY DURATION	Participation is anticipated to be approximately 37 days for each subject.
INVESTIGATIVE SITES OR COUNTRIES	This is a multi-center study to be conducted in the United States.
STUDY ENDPOINTS	**Primary endpoint** The primary endpoint is the PK profile (plasma), including: C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{∞}, MRT, M/P Ratio, CL/F, V/F. Comparative bioavailability ($F_{T/R}$) between the Test and Reference products will also be evaluated. **Secondary endpoints** The secondary endpoints are safety and tolerability: evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including blood pressure [BP], heart rate [HR], respiration rate [RR], body temperature and weight), and adverse events (AEs).
STATISTICAL METHODS SUMMARY	All subjects who receive at least one dose of APL-130277, APO-go®, or APOKYN® will be included in the safety analysis set. The PK analysis set includes all subjects with at least one PK evaluation. *Primary Objective:* AUC_{last}, AUC_{∞}, C_{max}, T_{max}, $t_{½}$, and λ_z will be evaluated. Analysis of Variance (ANOVA) will be performed for log-transformed AUC_{last}, AUC_{∞} and C_{max}. T_{max} will be analyzed using a non-parametric test (Wilcoxon test) while $t_{½}$ will be analyzed using a t-test. Comparative bioavailability will be assessed by estimating the 90% confidence intervals (CI) for the formulation ratios (APL-130277 vs. APO-go® vs. APOKYN®) of geometric means for AUC_{last}, AUC_{∞}, C_{max} and will be calculated based on the ratios of the least squares means and estimates from the ANOVA. *Secondary Objectives:* Safety and tolerability will be evaluated through summary tables and individual listings of all safety parameters collected in the study.

SAMPLE SIZE CALCULATION	With a sample size of 12 subjects, a two-sided 90% confidence interval for the difference in paired PK parameter means on the log scale will have an interval that extends no more than 0.221 units from the observed difference with 90% coverage probability. This calculation assumes a coefficient of variation of 35% for the difference on the original scale. If the observed mean difference on the log scale were zero, this would correspond to a 90% confidence interval for the ratio of geometric means of (80.2%, 124.7%) on the original scale.

4. STUDY DESIGN FLOW CHART

Table 1: Schedule of Events

Procedures	**Screening Visit[1]**	**Telephone Contact[2]**	**Wash-Out**	**Period 1 Visit**	**Telephone Contact[2]**	**Wash-Out**	**Period 2 Visit**	**Telephone Contact[2]**	**Wash-Out**	**Period 3 Visit**	**Telephone Contact[2]**	**Wash-Out**	**End of Study Visit**
Study Visit	**SV**	**TC**	**W/O**	**P1**	**TC**	**W/O**	**P2**	**TC**	**W/O**	**P3**	**TC**	**W/O**	**EOS**
	-21 to -3	**1 day prior to W/O**	**1 day prior to P1**	**1**	**1 day prior to W/O**	**1 day prior to P2**	**3-5 days after P1**	**1 day prior to W/O**	**1 day prior to P3**	**3-5 days after P2**	**1 day prior to W/O**	**1 day prior to EOS**	**3-5 days after P3**
Day	**-21 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-11**	**12**	**13**	**14-16**
Outpatient Visit	**X**			**X**			**X**			**X**			**X**
Written Informed Consent	**X**												
Reconfirmation of Consent				**X**			**X**			**X**			**X**
Review Entry Criteria	**X**												
Review Prohibited Treatment & Study Restrictions	**X**			**X**			**X**			**X**			**X**
Medical History/Demographics	**X**												
Complete Physical Exam, including Oropharyngeal Exam & Injection Site Reaction[3]	**X**												**X**
Abbreviated Physical Exam, including Oropharyngeal Exam & Injection Site Reaction[4]				**X**			**X**			**X**			
BMI, Weight and Height[5]	**X**			**X**			**X**			**X**			**X**

Procedures	**Screening Visit[1]**	**Telephone Contact[2]**	**Wash-Out**	**Period 1 Visit**	**Telephone Contact[2]**	**Wash-Out**	**Period 2 Visit**	**Telephone Contact[2]**	**Wash-Out**	**Period 3 Visit**	**Telephone Contact[2]**	**Wash-Out**	**End of Study Visit**
Study Visit	**SV**	**TC**	**W/O**	**P1**	**TC**	**W/O**	**P2**	**TC**	**W/O**	**P3**	**TC**	**W/O**	**EOS**
	-21 to -3	**1 day prior to W/O**	**1 day prior to P1**	**1**	**1 day prior to W/O**	**1 day prior to P2**	**3-5 days after P1**	**1 day prior to W/O**	**1 day prior to P3**	**3-5 days after P2**	**1 day prior to W/O**	**1 day prior to EOS**	**3-5 days after P3**
Day	**-21 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-11**	**12**	**13**	**14-16**
Vital Signs (BP, HR, RR and Temp)[6,7]	**X**			**X**			**X**			**X**			**X**
12-Lead ECG[7,8]	**X**			**X**			**X**			**X**			**X**
Clinical Laboratory Tests[9]	**X**												**X**
PK[7,10]				**X**			**X**			**X**			
MMSE	**X**												
Modified Hoehn and Yahr[11]	**X**												
C-SSRS[12]	**X**												**X**
Clinical Confirmation of "OFF" or full "ON"	**X**			**X**			**X**			**X**			
Randomization				**X**									
In-Clinic Dosing				**X**			**X**			**X**			
AEs/Serious AEs (SAEs)	**X**			**X**			**X**			**X**			**X**
Previous/Current Concomitant Medications	**X**			**X**			**X**			**X**			**X**

[1] All screening procedures to be conducted within 21 days prior to dosing (Period 1).
[2] Telephone contact as a reminder for subject to discontinue APOKYN® a minimum of 1-day prior to each study visit for the Wash-Out Interval (excluding SV).
[3] Physical examinations to include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth – oral cavity; musculoskeletal system; central and peripheral nervous system; skin; and injection site. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue. Examination for injection site reaction will be completed at the End of Study Visit (EOS).

[4] Abbreviated physical examinations to include head-eyes-ears-nose and throat; heart; lungs; abdomen; skin; mouth – oral cavity and injection site to be done at t = 0 (just prior to dosing) and 2 hours after dosing at Period 1, Period 2, and Period 3. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
[5] Both height and weight captured at the Screening Visit to calculate BMI; only weight captured at all other indicated visits.
[6] Vital signs will be assessed at the Screening Visit and End of Study Visit; Period 1, Period 2 and Period 3 at t = 0 minutes (just prior to dosing), 15, 45 and 60 minutes. Blood pressure to be measured supine and standing (measured within 3 minutes of standing) at all timepoints.
[7] Suggested Sequence of Assessments: PK – ECG – Vitals.
[8] 12-lead ECG: Obtain in triplicate at the Screening Visit. Period 1, Period 2 and Period 3 obtain at t = 0 (just prior to dosing) and 60 minutes after dosing. Obtain at the End of Study Visit.
[9] Blood and urine collection for clinical laboratory tests will occur at the Screening Visit and at the End of Study Visit. In addition, serum pregnancy test will be performed on all females of childbearing potential.
[10] PK will be assessed in Period 1, Period 2 and Period 3 at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes and 1.5, 3, 6 hours after dosing.
[11] The modified Hoehn and Yahr will be used during the Screening Visit in the "ON" state to determine eligibility.
[12] C-SSRS "Screening" scale to be used at the Screening Visit; "Since Last Visit" scale to be used at End of Study Visit.

5. TABLE OF CONTENTS

List of Tables

6. LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
$5HT_3$	5-hydroxy tryptophan (serotonin)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APO-go®	apomorphine hydrochloride injection marketed in the EU
APOKYN®	apomorphine hydrochloride injection marketed in the US
API	active pharmaceutical ingredients
AUC_{last}	area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve using the linear up log down trapezoidal rule.
AUC_{∞}	area under the concentration-time curve from time zero extrapolated to infinity using the linear up log down trapezoidal rule.
AST	aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	maximum observed plasma concentration
COMT	Catechol O-methyltransferase
CR	chronic release
CRA	Clinical Research Associate
CRF	case report form
CSA	clinical study agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation
ECG	electrocardiogram
EDC	electronic data capture
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

Abbreviation or specialist term	Explanation
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
L-Dopa	L-3,4-dihydroxyphenylalanine or Levodopa
λz	terminal-phase rate constant
MAO-B	monoamine oxidase B
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
MMSE	Mini-Mental State Examination
OH	Orthostatic Hypotension
PD	Parkinson's disease
PK	pharmacokinetic
QTc	Corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
RR	respiratory rate
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Sunovion	Sunovion Pharmaceuticals Inc.
$t_{½}$	Terminal-phase half-life
TdP	Torsades de Pointes
Temp	temperature
T_{max}	observed time of the maximum concentration
V/F	Apparent volume of distribution after non-intravenous administration

Abbreviation or specialist term	Explanation
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

7. INTRODUCTION

7.1. Background

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. PD has a prevalence of approximately 0.5% to 1% among persons 65 to 69 years of age, rising to 1% to 3% among persons 80 years of age and older (Tanner, 1996). The disease is characterized by progressive degeneration of the dopaminergic nigrostriatal system and depletion of dopamine, which results in the core motor symptoms of bradykinesia, rigidity, tremor, and postural instability (Hornykiewicz, 2008).

During the early stages of the disease, motor symptoms are well controlled with L-Dopa plus a dopamine decarboxylase inhibitors, dopamine agonists or MAO-B inhibitors. However, as the disease progresses, PD patients develop motor complications which consist of dyskinesia and motor fluctuations. Motor fluctuations represent periods of "OFF" time and include wearing "OFF", delayed "ON" (if with first morning dose termed morning akinesia), unexpected "OFF" or "ON"/"OFF" fluctuations. These motor fluctuations can be either predictable or unpredictable.

The mechanisms by which response fluctuations occur are only partially understood but are thought to include presynaptic neuronal degeneration leading to a lack of buffering of released L-Dopa, postsynaptic changes in dopamine receptor sensitivity and number, and pharmacokinetic and pharmacodynamic influences of exogenously administered dopaminergic agents (Mouradian, 1989; Stocchi, 2005). Fluctuations in plasma levels of L-Dopa occur due to the short half-life of L-Dopa and the unpredictable variability of gastric emptying.

In general, approximately 40% of patients with PD experience motor fluctuations and/or dyskinesias after 4 to 6 years of L-Dopa therapy, with close to 90% of patients experiencing these symptoms after 9 or more years of treatment (Ahlskog, 2001).

Predictable motor fluctuations (i.e. wearing "OFF") can be treated by increasing the dose or frequency of L-Dopa or by adding adjunctive Parkinson's disease medications (Catechol O-methyltransferase [COMT] inhibitors, MAO-B inhibitors, dopamine agonists). However, over time this becomes less effective. Treatment of unpredictable motor fluctuations (i.e. delayed "ON", Sudden "OFF", "ON"/"OFF" fluctuations) is limited. Some patients take oral L-Dopa immediate release as needed but this is of limited value as higher doses of L-Dopa can result in dyskinesia and perpetuates the development of further motor complications.

The only approved treatment for acute management of "OFF" episodes in the United States, Europe, Asia, and Canada is apomorphine dosed by subcutaneous (s.c.) injection. Although efficacious, s.c. apomorphine has limited use due to its parenteral administration and since it may be difficult for a PD patient to deliver. There remains a huge unmet medical need for easy to administer, rapid, safe, effective and reliable rescue medications for the treatment of these "OFF" episodes in PD patients. APL-130277, sublingually administered apomorphine, provides a more patient-friendly, easy to administer medication for the management of both predictable and unpredictable "OFF" episodes.

Apomorphine is a non-ergot dopamine agonist that binds to D_1-like and D_2-like receptors. First used as a treatment for PD as early as 1951, its clinical use was first reported in 1970 although its

emetic properties and short half-life made oral use impractical. A later study found that combining the drug with 10 mg domperidone improved results significantly (APOMORPHINE, 1949; Cotzias, 1970; Corsini, 1979; Millan, MJ; Schwab, 1951).

Apomorphine hydrochloride injection is a prescription medicine that reverses “OFF” episodes (end-of-dose wearing-“OFF” and unpredictable “ON”-“OFF” episodes) associated with advancing PD. The injectable form of apomorphine hydrochloride is marketed in the United States as APOKYN®, in Canada as MOVOPO™ and in most of Europe and Asia as APO-go®.

APOKYN® (apomorphine hydrochloride injection, see Section 19.1) is indicated for the acute, intermittent treatment of hypomobility, “OFF” episodes associated with advanced PD, has been studied as an adjunct to other PD medications. Therapeutic use in PD is effective because of the drug's strong dopaminergic action. Within 3-20 minutes of injection, apomorphine demonstrates a magnitude of effect (ability to convert the patient with PD to the “ON” state) that is comparable to L-Dopa. The effects of a single s.c. injection last for 60 minutes. Apomorphine can be used in combination with L-Dopa. L-Dopa dosing may need to be readjusted (decreased) to reduce dopa-induced dyskinesias periods (APOMORPHINE, 1949; Cotzias, 1970; Corsini, 1979; Millan, MJ; Schwab, 1951).

Subcutaneous injection of apomorphine was developed to avoid first-pass metabolism as apomorphine is almost completely metabolized when delivered orally (between 1-2% of the total dose enters the bloodstream following oral administration). The total daily dose can range up to 20-25 mg/daily.

7.2. Drug Substance

The active ingredient is apomorphine hydrochloride hemihydrate ($C_{17}H_{17}NO_2$•HCl•½H_2O(salt)). Apomorphine is synthesized from morphine, but it is not a narcotic, nor is it a controlled substance. Apomorphine hydrochloride appears as white or greyish-white glistening crystals or white powder. The R-enantiomer is used clinically.

The drug substance, apomorphine hydrochloride hemihydrate is manufactured by Sanofi-Aventis. Apomorphine hydrochloride is manufactured from morphine monohydrate in the presence of orthophosphoric acid, ethyl acetate and hydrochloric acid. Purification is performed in the presence of water, sodium chloride, sodium sulfite, ethyl acetate and silica gel.

A summary of physico-chemical data are provided in Table 2.

Table 2: Summary of Apomorphine Physico-Chemical Data

Active Pharmaceutical Ingredients (API) Common Name	Apomorphine Hydrochloride Hemihydrate
Production Site	Manufacturer of Active Pharmaceutical Ingredient for Clinical Batches: Sanofi Aventis (Aramon Site) SANOFI CHIMIE Route d'Avignon 30390 Aramon France
IUPAC nomenclature	4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate
Synonyms, common names	Apomorphine hydrochloride, SR94013A, 6a,beta-aporphine-10,11-diol hydrochloride
CAS number	41372-20-7
Formula	$C_{17}H_{17}NO_2 \bullet HCl \bullet {}^1/_2H_2O$
Molecular weight	312.79 g/mol
Specific Rotation	-60.5^o to -63.0^o
pKa	pKa: 7.0, 8.9
pH	4.3
Water solubility	Sparingly soluble in water and alcohol; slightly soluble in chloroform

7.3. Drug Product (APL-130277 Sublingual Thin Film)

The product under development, APL-130277, is a soluble thin film for sublingual administration. APL-130277 is designed to deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first pass metabolism associated with gastrointestinal absorption of the compound. The product is intended to be an alternative to the injectable form of apomorphine hydrochloride, which is marketed in the United States as APOKYN® and in most of Europe and Asia as APO-go®.

APL-130277 is manufactured for clinical studies as a bilayer thin film with one layer containing the active ingredient, apomorphine hydrochloride, and the other layer containing a buffer (pyridoxine). Dosage units of 10, 15, 20, 25, and 30 mg are achieved from a single formulation by cutting different sized rectangular thin films from sheets of bulk film as shown in the table below. Identifying marks are printed in white ink on the buffer side of the sublingual thin film.

Table 3: Physical Characteristics of APL-130277

Apomorphine Hydrochloride Loading (mg)	Length (mm)	Width (mm)	Area (mm^2)	Identifying Mark
10	22	8.8	193.6	C1
15	22	13.2	290.4	C2
20	22	17.6	387.2	C3
25	22	22	484.0	C4
30	22	26.4	580.8	C5

The APL-130277 finished drug product will be manufactured at ARx, LLC facilities at: 400 Seaks Run Road Glen Rock, PA 17327, USA.

The formulations for each of the dosage strengths have exactly the same proportions of active pharmaceutical ingredient and inactive excipients.

The formulation consists of pharmaceutically acceptable cellulosic film formers along with glycerin as a plasticizer; and flavor, sweetener and colour additives for patient acceptability. Other excipients include sodium hydroxide to modify pH and sodium metabisulfite as an antioxidant/preservative. The formulation also includes pyridoxine HCL as a buffer component. The excipients used in formulating APL-130277 sublingual thin films, are compendial (USP, NF or FCC) items and/or are Generally Recognized as Safe (GRAS) and/or have precedent for use in pharmaceutical products approved in the US.

7.4. Clinical Experience

This is the thirteenth planned in-man study for APL-130277. Previous studies CTH-101, CTH-102, CTH-103, CTH-104, CTH-106, CTH-107 and CTH-200 were performed in healthy volunteers in Malaysia, all at Info Kinetics. CTH-101 through CTH-104 and CTH-107 were conducted with prototype formulations. The first study completed in a PD patient population, CTH-105, was conducted at 4 sites in North America. CTH-300 and CTH-301, both evaluating APL-130277 in a PD patient population, are being conducted concurrently in North America. CTH-201 and CTH-302 are planned in a PD patient population and will be conducted in Europe in early 2017.

The clinical experience with APL-130277 in healthy volunteers is summarized in considerable detail in the Investigator's Brochure (IB). Adverse events were those expected to be seen with apomorphine, with the most common AEs being somnolence, dizziness and nausea. No dose limiting side effects were encountered with APL-130277 and no subjects discontinued APL-130277 treatment due to AE.

The healthy volunteer studies confirmed the method of administration, allowed further refinement of the formulation and confirmed PK comparability of APL-130277 to s.c. apomorphine. The CTH-103 and CTH-104 PK study results demonstrated dose proportionality of the doses of APL-130277 tested (10 mg, 15 mg, 25 mg) and that the 25 mg dose is sustained over an extended period of time (162 minutes) above the minimal efficacious plasma concentration of apomorphine (approximately 3 ng/mL), believed to be a level demonstrating

symptomatic relief of "OFF" symptoms. The T_{max} for the 25 mg dose of APL-130277 was approximately 40 minutes, which was similar for the 10 mg and 15 mg doses of APL-130277. The rapid uptake of apomorphine in the APL-130277 sublingual thin film is comparable to that described in the s.c. apomorphine labels (ie, between 10 and 60 minutes).

The PD subjects dosed in CTH-105 (19 subjects) displayed similar side effects to that seen in healthy volunteers; the most common AEs (seen in 2 or more subjects) were dizziness, somnolence, nausea, yawning, headache and hyperhidrosis. Most of these AEs were mild to moderate in severity. There was no dose-response relationship seen with the most common AEs and no subjects discontinued due to an AE. Local irritation of the oral mucosa was monitored in the study and none was noted.

The CTH-105 study demonstrated that APL-130277 provided rapid, clinically meaningful improvement in MDS-UPDRS Part III scores for PD subjects in the "OFF" state and converted most subjects from the "OFF" state to the "ON" state. Much of the benefit was sustained through 90 minutes. A range of doses were utilized but over half of the subjects responded to the two lowest doses (10 and 15 mg).

The CTH-106 study results demonstrated that the orientation of the thin film does not have a meaningful impact on the bioavailability of apomorphine.

In CTH-107 and CTH-200, similar AEs were seen as in the previous healthy volunteer studies, and study analysis is ongoing.

7.5. Summary of Potential Risks and Benefits

Given that APL-130277 uses the same active pharmaceutical ingredient (API) as APO-go® and APOKYN®, and the pharmacokinetic profile is comparable between the sublingual thin film and the s.c. injection, the risks associated with the drug will be the same as those seen in the APOKYN® and APO-go® Product Inserts (see Section 19.1 and Section 19.3), except for the injection site reactions. It is assumed that the bioavailability of APL-130277 will be consistent in CTH-203 with that found in previous experience with APL-130277 compared with APO-go® and APOKYN®.

The buffer contained in the inactive layer of APL-130277 is designed to mitigate potential irritation of the oral mucosa seen in other buccal formulations of apomorphine as well as assist in maintaining a stable pH and optimal absorption kinetics. A preclinical hamster study demonstrated no evidence of microscopic or macroscopic irritation and there have been no reports of local irritation in any of the human studies to date. No local irritation was noted in the CTH-105 study, and despite the anticipated low risk of local irritation in this study, local irritation will be monitored. The goal of this development program, however, is to formulate a medication that provides the PD patient with an easier delivery system. We hypothesize that an orally available formulation will be easier to use, allow quicker control over predicted "OFF" periods, be more readily accessible to the patient when unpredicted "OFF" episodes occur during activities of daily living, and potentially be used by the milder PD patient when "OFF" episodes begin during the advancement of the disease.

7.6. Rationale

This multi-center, Phase 2 study is designed to evaluate the pharmacokinetics (PK) and comparative bioavailability of a single dose of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD) who experience motor fluctuations ("OFF" episodes).

8. ETHICS

This study will be conducted in compliance with the principles established by the World Medical Assembly in the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects and all applicable amendments, the ICH Principles of Good Clinical Practice (GCP) (including archiving of essential study documents), and applicable regulatory requirements and guidelines.

A properly constituted, valid Institutional Review Board (IRB) or Research Ethics Board (REB) or Independent Ethics Committee (IEC) must review and approve the protocol, each Investigator's Informed Consent Form (ICF), and related subject information before the start of the study, and any subject recruitment material(s) before they are provided to subjects. During the Clinical Trial, any amendment or modification to the protocol should be submitted to the IRB/REB/IEC. The IRB/REB/IEC should also be informed of any event likely to affect the safety of subjects or the continued conduct of the study, in particular any changes in safety. All updates to the IB will be sent to the IRB/REB/IEC.

It is the responsibility of each Investigator to ensure that written informed consent is obtained from the patient before any study activity or procedure is undertaken.

9. OBJECTIVES AND STUDY ENDPOINTS

9.1. Objectives

The primary objective is to evaluate the pharmacokinetics (PK) and comparative bioavailability of a single dose of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD) complicated by motor fluctuations ("OFF" episodes).

The secondary objective is to evaluate the safety and tolerability of the study drugs.

9.2. Study Endpoints

9.2.1. Primary Endpoint

PK profile (plasma), including: C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{∞}, MRT, M/P Ratio, CL/F, V/F. **C**omparative bioavailability ($F_{T/R}$) between the Test and Reference products will also be evaluated.

9.2.2. Secondary Endpoints

Safety and tolerability: evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including blood pressure [BP], heart rate [HR], respiration rate [RR], body temperature and weight), and adverse events (AEs).

10. STUDY DESIGN

This is a multi-center, phase 2, open-label, randomized, three-way crossover study designed to evaluate the pharmacokinetics (PK) and comparative bioavailability of a single dose of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD).

10.1. General Overview

This study will commence with an initial Screening Visit, followed by an open-label, randomized, three-way crossover (Period 1, Period 2, and Period 3). Subjects will receive all three treatment arms with a minimum 1-day Wash-Out Interval between each visit (excluding the screening visit).

10.2. Screening Visit

Before any study procedures are performed on any person, informed consent must be obtained. Subjects, who have provided full consent to participate, will arrive at the clinic having taken their usual morning dose of PD medications; but before taking their next dose of medication. Their normally scheduled second dose of L-Dopa (without adjunctive PD medication) will be administered in the clinic following confirmation of an "OFF" episode by the Investigator, to ensure the subject experiences an "ON" response. Eligibility criteria will be assessed by the Investigator. Subjects, who are considered eligible, will be scheduled for the Period 1 Visit.

10.3. Wash-Out Interval

One (1) day before each Period Visit, at a minimum, subjects will be required discontinue subcutaneous APOKYN®; this is referred to as the wash-out interval. L-Dopa and any other adjunctive PD medication will be permitted during this time.

10.4. Three-Way Open-Label Randomized Crossover (Period 1, Period 2, Period 3)

Subjects will be asked to return to the clinic the morning of Period 1 (P1) after their usual morning dose of PD medications; but before taking their next dose of medication and will be randomized to one of the 6 treatment sequences.

Subjects will be required to wait to take their normally scheduled second dose of PD medications until after confirmation by the Investigator that the subject is in the "OFF" state and will be dosed according to the randomized treatment sequence with APL-130277, APO-go®, or APOKYN®. All PD medications should be held until 60 minutes after dosing.

Following the same procedures described above, subjects will return to clinic within 3-5 days after Period 1 and will be dosed for Period 2 with one of the other two treatments. Subjects will return to clinic within 3-5 days after Period 2 and will be dosed for Period 3 with the third and last treatment.

10.5. Randomized Treatment Sequence

Subjects will be randomly assigned to one of the sequences shown in Table 4.

Table 4: Randomized Treatment Sequences

	Period 1	Period 2	Period 3
Sequence 1	APL-130277	APOKYN®	APO-go®
Sequence 2	APL-130277	APO-go®	APOKYN®
Sequence 3	APOKYN®	APL-130277	APO-go®
Sequence 4	APOKYN®	APO-go®	APL-130277
Sequence 5	APO-go®	APL-130277	APOKYN®
Sequence 6	APO-go®	APOKYN®	APL-130277

Treatment Arms:

- APL-130277 sublingual thin film
- Subcutaneous APO-go®
- Subcutaneous APOKYN®

10.6. Dosing Algorithm

APL-130277 and APO-go® dosing in the Three-Way Crossover will be based on the subjects' current prescribed dose of APOKYN®, as shown in Table 5.

Table 5: Dosing Algorithm

APOKYN® Current Prescribed Dose	APO-go® Study Dose	APL-130277 Study Dose*
2 mg	2 mg	15 mg
3 mg	3 mg	20 mg
4 mg	4 mg	25 mg
5 mg	5 mg	30 mg

**These are approximate equivalent doses based on PK.*

11. PATIENT POPULATION

11.1. Selection of Study Population

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site.

The study will require approximately 12 subjects to complete the Three-Way Crossover phase. Recruitment will continue until the required number of subjects complete the study.

11.1.1. Inclusion Criteria

Patients who meet each of the following criteria will be eligible for participation in the study:

1. Male or female ≥ 18 years of age.
2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion).
3. Clinically meaningful response to Levodopa (L-Dopa) with well-defined "OFF" episodes, as determined by the Investigator.
4. Receiving APOKYN® of ≤ 5 mg per dose for at least 4 weeks before the Screening Visit.
5. Receiving stable doses of L-Dopa/carbidopa (immediate or sustained release) administered at least 4 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the Screening Visit. Adjunctive PD medication regimens must be maintained at a stable dose for at least 4 weeks prior to the Screening Visit with the exception that MAO-B inhibitors must be maintained at a stable level for at least 8 weeks prior to the Screening Visit.
6. No planned medication change(s) or surgical intervention anticipated during the course of study.
7. Patients must experience a well-defined "OFF" episode in the morning if they do not take their morning PD medications on schedule, and must be willing to delay morning doses on the 3 study dosing days.
8. Stage III or less on the modified Hoehn and Yahr scale in the "ON" state.
9. Mini–Mental State Examination (MMSE) score > 23.
10. If female and of childbearing potential, must agree to use one of the following methods of birth control:
    - Oral contraceptive;
    - Contraceptive patch;
    - Barrier (diaphragm, sponge or condom) plus spermicidal preparations;
    - Intrauterine contraceptive system;
    - Levonorgestrel implant;

- Medroxyprogesterone acetate contraceptive injection;
- Complete abstinence from sexual intercourse;
- Hormonal vaginal contraceptive ring; or
- Surgical sterilization or partner sterile (must have documented proof).

11. Male patients must be either surgically sterile, agree to be sexually abstinent or use a barrier method of birth control (eg, condom) or maintain a monogamous relationship with a person who is not of child-bearing potential from first study drug administration until 30 days after final drug administration.
12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
13. Able to understand the consent form, and to provide written informed consent

11.1.2. Exclusion Criteria

Patients will be excluded from participation in the study for any of the following reasons:

1. Atypical or secondary parkinsonism.
2. Previous treatment with any of the following: continuous subcutaneous (s.c.) apomorphine infusion; or Duodopa/Duopa.
3. Contraindications to APO-go® or APOKYN® or hypersensitivity to apomorphine hydrochloride or any macrolide antibiotic or any of the ingredients of APO-go® or APOKYN® (notably sodium metabisulfite).
4. Female who is pregnant or lactating.
5. Participation in a clinical trial within 30 days prior to the Screening Visit.
6. Receipt of any investigational (ie, unapproved) medication within 30 days prior to the Screening Visit.
7. Any selective 5HT3 antagonists (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (excluding quetiapine and clozapine) or dopamine depleting agents within 30 days prior to the Screening Visit.
8. Drug or alcohol dependency in the past 12 months.
9. History of malignant melanoma.
10. Clinically significant medical, surgical, or laboratory abnormality in the opinion of the Investigator.
11. Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis, or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.
12. History of clinically significant hallucinations during the past 6 months.
13. History of clinically significant impulse control disorder(s).

14. Dementia that precludes providing informed consent or would interfere with participation in the study.
15. Current suicidal ideation within one year prior to the Screening Visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 5 years.
16. Donation of blood plasma in the 30 days prior to first dosing.
17. Cankers or mouth sores within 30 days prior to the Screening Visit, or other clinically significant oral pathology in the opinion of the Investigator. The Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling a patient into the study.

11.2. Prior and Concomitant Treatments

11.2.1. Prohibited Treatments

The following prior and/or concomitant treatments will not be allowed during the course of this study:

- Treatment with any form of s.c. apomorphine other than study medication(s).
- Any selective 5HT3 antagonist (eg, ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to the Screening Visit until study completion.
- Any dopamine antagonists or dopamine depleting drugs excluding quetiapine or clozapine.
- Deep brain stimulation or other neurosurgical procedure for the treatment of PD.
- Continuous s.c. apomorphine infusion.
- Duodopa/Duopa.
- Use of an anti-emetic is not permitted. In cases where a subject is presently using an anti-emetic they will be allowed to continue with this treatment at the prescribed dose.

11.2.2. Permitted Treatments

The following concomitant treatments will be allowed during the course of the study and will be coded using WHO DD:

- Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies (from at least 4 weeks prior to the Screening Visit, with no planned medication changes during the study).
- Any other medication other than those identified in Section 11.2.1 are allowed, provided they are stable, with no planned medication changes scheduled during the study. Other therapies should only be administered as necessary for the treatment of the subject, at the discretion of the Investigator. All concomitant medications must be recorded in the appropriate Case Report Form (CRF) for the subject.

11.3. Subject Withdrawal from the Study

Subjects may be withdrawn from participating in this study for the following:

- In order to protect their safety and/or well-being;
- If they are unwilling or unable to comply with required study procedures;
- If they withdraw their consent to participate in the study;
- If the study is prematurely terminated by the Sponsor or Regulatory Authorities;
- If they no longer meet the inclusion/exclusion criteria within the study.

Subjects will be advised that they are free to withdraw from the study at any time, for any reason, and without prejudice. Every reasonable and appropriate effort should be made by the Investigator to keep subjects in the study. However, subjects must be withdrawn from the study if the subject withdraws his or her consent to participate. In the event of subject withdrawal, the Investigator should attempt to determine the reason for the subject's withdrawal.

The reason for discontinuation and the date of withdrawal from the study will be recorded in the appropriate CRF. The Investigator should make at least 3 documented attempts to contact a subject who is lost to follow-up, with at least 1 attempt made by a certified letter. Documentation of contact attempts must be made in the subject's record.

Neither subjects withdrawing from the study nor those removed by the Investigator or Sponsor will be replaced. Subjects who are withdrawn from this study may not re-enter the study at a later date. The screening number for a withdrawn subject will not be reassigned to another subject.

If a subject is removed or withdraws from the study, the procedures outlined in the EOS Visit will be performed, where possible.

12. STUDY PROCEDURES

This study will consist of the following:

1. Screening Visit (SV)
2. Telephone Contact
3. Wash-Out Interval
4. Three-Way Open-Label Randomized Crossover
    a. Period 1 Visit (P1)
    b. Period 2 Visit (P2)
    c. Period 3 Visit (P3)
5. End of Study Visit (EOS)

12.1. Screening Visit

Potential subjects must sign an Informed Consent Form (ICF) before any screening-related procedures are performed. Subjects, who have provided full consent to participate, will arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Their normally scheduled second dose of L-Dopa (without adjunctive PD medication) will be administered in the clinic following confirmation of an "OFF" episode by the Investigator, to ensure the subject experiences an "ON" response.

The following procedures will be performed by study staff at the Screening Visit:

- Review the study and obtain written informed consent. Subjects may review the consent and return it at a later date, at which time the Screening Visit will take place.
- Review inclusion/exclusion criteria.
- Record demographics and detailed medical history, including review of medications taken within 6 months prior to the Screening Visit, current treatment regimens, drug, alcohol and smoking history.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure height and weight; calculate BMI.
- Record vital signs (BP, HR, RR and Temp), after the subject has been in a supine position for 5 minutes. Subject BP to be measured both supine and standing (within 3 minutes of standing).
- Perform a standard 12-lead ECG in triplicate.
- Collect blood and urine sample for clinical laboratory tests (hematology, chemistry, urinalysis and serology). Serum pregnancy test for females of child-bearing potential only.

- Perform a MMSE.
- Assess subject using the Modified Hoehn and Yahr scale (for a sample, see Section 19.5).
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). The "Screening" scale should be used at this visit.
- Investigator confirmation of "OFF" or "ON". The subject must be in an "OFF" state prior to dosing to ensure they experience an "ON" response.
- When subject is in the "OFF" state, dose subject with their normal dose of L-Dopa without their normal adjunctive PD medication.
- Record any AEs/SAEs that have occurred after the informed consent was obtained.

The Investigator will review all information obtained from the screening procedures. If the subject is not eligible, the subject will be a screening failure and will not attend any other visits. Subjects who fulfill all entry criteria will be found eligible to participate in the trial and an appointment for the Period 1 Visit (P1) will be made.

12.2. Wash-Out Interval

One (1) day before each Period Visit, at a minimum, subjects will be required discontinue subcutaneous APOKYN®; this is referred to as the wash-out interval. L-Dopa and any other adjunctive PD medication will be permitted during this time.

12.3. Telephone Contact

One (1) day before the Wash-Out Interval (ie, 2 days before the Period Visit), the site staff will contact subjects as a reminder to discontinue subcutaneous APOKYN® one (1) day prior to each Period Visit.

12.4. Three-Way Open-Label Randomized Crossover (Period 1, Period 2, Period 3)

Subjects will be asked to return to the clinic the morning of Period 1 (P1) after their usual morning dose of PD medications; but before taking their next dose of medication and will be randomized to one of the 6 treatment sequences.

Subjects will be required to wait to take their normally scheduled second dose of PD medications until after confirmation by the Investigator that the subject is in the "OFF" state and will be dosed according to the randomized treatment sequence with either APL-130277, APO-go®, or APOKYN®. Subjects will receive all three treatment arms with a minimum 1-day Wash-Out Interval between each visit.

Following the same procedures described above, subjects will return to clinic within 3-5 days after Period 1 and will be dosed for Period 2 with one of the other two treatments. Subjects will return to clinic within 3-5 days after Period 2 and will be dosed for Period 3 with the third and last treatment.

The following procedures will take place at these visits, except where explicitly noted:

- Reconfirm consent.
- Review prohibited treatment and study restrictions.
- Perform randomization (at the Period 1 Visit only).
- Perform an abbreviated physical examination, including oropharyngeal examination and of the injection site at t = 0 (just prior to dosing) and 2 hours after dosing. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure body weight.
- Perform a standard 12-lead ECG t = 0 (just prior to dosing) and approximately 60 minutes after dosing.
- Record vital signs (BP, HR, RR and Temp) at t = 0 minutes (just prior to dosing), and at 15, 45, and 60 minutes after dosing. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Collection and processing of blood samples for PK assessment will occur at the following time points: t = 0 (just prior to dosing), 15, 30, 45, and 60 minutes after dosing and at 1.5, 3, and 6 hours after dosing.
- Investigator confirmation of "OFF" or "ON". The subject must be in an "OFF" state in order to proceed with dosing.
- When subject is in the "OFF" state, proceed with dosing according to the randomization scheme.
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

If in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (+/- other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until 60 minutes after dosing.

12.5. End of Study Visit

Approximately 3-5 days following the completion of the study (after Period 3), subjects will be asked to return to the clinic for a final safety assessment visit having completed a 1-day wash-out prior to this visit. The following procedures will take place at this visit:

- Reconfirm consent.
- Review prohibited treatment and study restrictions.
- Perform a complete physical examination, including an oropharyngeal examination and of the injection site. The oropharyngeal cavity examination should include a

visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

- Measure body weight.
- Perform a standard 12-lead ECG.
- Record vital signs (BP, HR, RR and Temp), after the subject has been in a supine position for 5 minutes. Subject BP to be measured both supine and standing (within 3 minutes of standing).
- Collect blood and urine sample for clinical laboratory tests (hematology, chemistry, urinalysis). Serum pregnancy test for females of child-bearing potential only.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). The "Since Last Visit" scale should be used at this visit.
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

12.6. Duration of Treatment

The duration of participation, from screening until final study completion, is approximately 37 days.

12.7. Assessments

12.7.1. Order of Assessments

When assessments occur at the same timepoint, the order of assessments should be:
PK –> ECG –> Vitals.

12.7.2. Clinical Safety Assessments

12.7.2.1. Physical Examinations

Complete physical examinations at all scheduled timepoints must include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including the oral cavity; musculoskeletal system; central and peripheral nervous system; skin; and the injection site (End of Study Visit only). The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue. To be done at the Screening Visit and End of Study (EOS) Visit.

Abbreviated physical examinations at all scheduled timepoints must include head-eyes-ears-nose and throat; heart, lungs; abdomen; skin; and the injection site. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue. To be done at t = 0 (just prior to dosing) and 2 hours after dosing in Period 1, Period 2, and Period 3.

All physical examinations performed in this study, whether complete or abbreviated, will include an oropharyngeal cavity examination by the Investigator (or designate trained to perform this examination) and will include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue. Each location within the oropharyngeal examination will be scored and graded as follows:

- Finding
  - None
  - Focal reddening
  - Multiple foci of reddening
  - Edema
  - Ulceration
- Grade
  - Mild
  - Moderate
  - Severe

All abnormal findings at baseline will be recorded on the Medical History/Concomitant Diagnoses page (or equivalent) of the CRF. New abnormal findings or a worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the CRF.

The Investigator (or designate) should evaluate each finding against AE criteria and complete the AE CRF, as appropriate. Photographs for reference may be taken by the Investigator (or designate) provided the subject provides consent to do so.

12.7.2.2. Vital Signs

Vital signs (HR, RR, BP and body temperature) will be measured at various timepoints after the subject has been in a supine position for 5 minutes. Vital signs will be measured at the Screening Visit and End of Study Visit. In Period 1, Period 2 and Period 3 at t = 0 (just prior to dosing), 15, 45 and 60 minutes after dosing at all scheduled study visits. Vital signs (BP only) will also be measured within three minutes of standing at all timepoints.

Study personnel will carefully monitor subjects for signs of Orthostatic Hypotension; defined as:

- a systolic BP decrease of ≥ 20 mmHg within three minutes of standing up from a supine position; and/or
- a diastolic BP decrease of ≥ 10 mmHg within three minutes of standing up from a supine position.

12.7.2.3. 12-Lead ECG

A standard 12-lead ECG will be performed at all timepoints outlined in the protocol. A triplicate 12-lead ECG will be performed at the Screening Visit.

ECGs will be performed in a semi-recumbent position and after 5 minutes of rest.

The following parameters will be collected:

- Heart rate
- PR interval
- QRS interval
- RR interval
- QT interval
- QTc Interval (Fridericia's correction)
- QTc Interval (Bazett's correction)

All ECGs should be assessed by the Investigator and deemed "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant". Abnormal readings that, in the opinion of the Investigator are deemed clinically significant should be reported as AEs on the appropriate CRF page.

12.7.2.4. Modified Hoehn and Yahr

The Modified Hoehn and Yahr scale will be administered at the Screening Visit to verify subjects meet the eligibility criteria for this study. This will be conducted in the "ON" state (for a sample, see Section 19.5).

12.7.2.5. Mini-Mental State Examination

Mini-Mental State Examination (MMSE) is used to evaluate a person's cognitive and mental function and will be administered at the Screening Visit to verify subjects meet the eligibility criteria for this study.

12.7.2.6. Clinical Laboratory Tests

The following clinical laboratory test samples will be collected where documented:

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count including differential.
Serum Chemistry:	albumin, total bilirubin, total protein, alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, creatinine, glucose, sodium, potassium, uric acid, globulin, vitamin B6. Serum pregnancy test will be performed on all females of child-bearing potential only.
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones.

Serology (at the Screening Visit only):	Human immunodeficiency virus (HIV), Hepatitis B surface antigen, Hepatitis C antibodies.

12.7.2.7. Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all personnel involved in the drawing of blood and the handling of specimens in both the clinic and laboratory settings.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples may be outlined in the study Laboratory Manual. It is the responsibility of the Investigator to ensure all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Blood and urine samples for hematology, serum chemistry, urinalysis, and serology will be sent to a central laboratory for analyses. Please see the Laboratory Manual for details.

12.7.2.8. C-SSRS

Formal assessments of subject suicidal ideation and behavior will be assessed at the Screening Visit and at the End of Study Visit (EOS). A final assessment will be performed at the time of termination, regardless if it is scheduled (ie, at EOS) or an early termination/withdrawal (for a sample, see Section 19.6).

12.7.2.9. Medical History

At the Screening Visit, the Investigator (or designate) will review the subject's medical history in order to ascertain the subject's eligibility. The medical history should assess the subject's current PD medications, including medication name, dose, number of tablets per dose (if applicable), dosage units and frequency per day.

The medical history assessment will include a detailed assessment of the subject's PD history, including, but not limited to:

- Year of diagnosis;
- Presence of a rest tremor at the time of diagnosis;
- Year when motor fluctuations began;
- Type of "OFF" episodes experienced (eg, morning akinesia, wearing-"OFF", delayed "ON", dose failure, sudden "OFF");
- Number of "OFF" episodes per day;
- Typical length of "OFF" episodes.
- PD medications previously or currently taken, including:
  - Dopamine agonists;

- MAO-B inhibitors;
- COMT inhibitors;
- Amantadine;
- Anti-cholinergics.

12.7.2.10. Confirmation of "OFF" or "ON" Episodes

At the Screening Visit, subjects will present to the clinic having taken their usual morning dose of L-Dopa and any other adjunctive PD medication; but before taking their next dose of medication. Their normally scheduled second dose of L-Dopa (without adjunctive PD medication) will be administered in the clinic.

Prior to administration of their L-Dopa dose, subjects will be examined by the Investigator in order to verify that they are in the "OFF" state. If they are in the "OFF" state, subjects will then take their normal dose of L-Dopa and the Investigator will as well determine that the subject is experiences an "ON" state. Confirmation of "OFF"/"ON" state should be noted in the appropriate eCRF.

Definitions of Full "ON" and "OFF"

The following definitions will be used in this study:

"OFF" – defined as:

- A period of time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness;
- Confirmed by the Investigator using their clinical judgement as "OFF".
- Confirmed by the subject as "OFF".

Full "ON" as assessed by the Investigator – defined as:

- Based on clinical judgment, it is the period of time where the Investigator feels the medication is providing benefit with regard to mobility, stiffness and slowness and the subject has adequate motor function to allow them to perform their normal daily activities.

Clinical confirmation of the "OFF" state must occur prior to dosing a subject with study medication (or their standard L-Dopa dose at the Screening Visit). The same assessor should be utilized for each subject throughout the study.

12.7.2.11. Pharmacokinetic (PK) Evaluation

Pharmacokinetic evaluation of APL-130277, subcutaneous APO-go® and APOKYN® will be completed in Period 1, Period 2, and Period 3. Blood draws for PK analyses will occur at t = 0 (just prior to dosing), 15, 30, 45, and 60 minutes after dosing and at 1.5, 3, and 6 hours after dosing. Sampling should occur as close as possible to the target time. Actual sampling date and time should be recorded in CRF.

Instructions specific to PK draws, sample preparation, storage and shipping will be outlined in the Pharmacokinetic Laboratory Manual.

13. ADVERSE EVENTS

Adverse events will be recorded from the time of signing of the ICF by the subject through to study completion or earlier, if warranted by a subject discontinuation. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

13.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a subject (or patient) or clinical investigation subject (or patient) administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition.

13.2. Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening;
- Requires in-subject hospitalization (being admitted) or prolongation of existing hospitalization;
- Results in permanent (persistent) disability/incapacity;
- Is a congenital anomaly;
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as **important medical events** that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject (or patient) or may require intervention to prevent another of the outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the investigational drug, or a hospital admission for a diagnostic evaluation of an AE, **does not** qualify the condition or event as an SAE.

A spontaneous abortion or congenital anomaly in an infant born to a mother who was exposed to the investigational drug during pregnancy **is** an SAE.

Due to the nature of subjects being enrolled in this study, and the given study objectives, for subjects who are hospitalized to facilitate their study visit, "OFF" episodes <u>will not</u> be considered a SAE.

13.3. Definition of Severity

The clinical "severity" of an AE will be classified as:

Mild	Causes no limitation of usual activities.
Moderate	Causes some limitation of usual activities.
Severe	Prevents or severely limits usual activities.

13.4. Definition of Start Date, Stop Date, and Duration

Start Date	The date at which the AE is first noted.
Stop Date	The date at which the AE is known to be resolved. If it is not known to have stopped, then indicate "ongoing".
Duration	A time in days, hours or minutes (this is optional).

13.5. Action(s) Taken

Actions taken may consist of:

None	No actions taken.
Discontinued Investigational Drug	Investigational drug was permanently discontinued because of the AE.
Change Investigational Drug	Investigational drug was given at a lower dose, at a longer interval between doses, or was temporarily withheld because of the AE.
Treatment	Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure.
Others	Other actions, such as an operative procedure, were required because of the AE.

13.6. Definition of Expectedness

An expected AE is an AE for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE is an AE for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and (b) hepatitis with a first occurrence of fulminate hepatitis.

13.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for APL-130277 are those pertaining to:

- Hypotension, orthostatic hypotension
- Syncope
- Falls & injuries
- Dyskinesias
- Hallucinations and psychotic behaviors
- Impulse control
- Daytime sudden onset of sleep
- QT prolongation and ventricular arrhythmias
- Acute Coronary Syndrome, myocardial infarction, angina
- Suicidal ideation & attempts
- Melanoma
- Stomatitis, oral ulcers, oral irritation
- Allergic/sensitivity response to the formulation

All AESIs should be reported to Sunovion as outlined in Section 13.13.

13.8. Definition of Relationship to Investigational Drug(s)

The categories for classifying the Investigator's opinion regarding the relationship of an AE to investigational drug(s) are listed below:

Certain	An AE occurring in a plausible time relationship to investigational drug administration and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Probable (likely)	An AE with a reasonable time sequence to administration of the investigational drug and which is unlikely to be attributed to concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Possible	An AE with a reasonable time sequence to administration of the investigational drug, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Unlikely	An AE, including laboratory test abnormality, with a temporal relationship to investigational drug administration that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Not related	An AE with sufficient evidence to accept that there is no causal relationship to investigational drug administration (eg, no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven; etc.).

13.9. Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Resolved;
- Resolved with sequelae;
- Ongoing;
- Death;
- Unknown.

Death should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for the AE attributed as the cause of death in the death certificate or summary.

13.10. Documentation of Adverse Events

The Investigator will monitor and/or ask about or evaluate AEs using non-leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term;
- When the AE first occurred (start date);
- When the AE stopped (stop date), or an indication of "ongoing";
- How long the AE persisted (optional);
- Severity of the AE;
- Seriousness;
- Actions taken;
- Outcome;
- Investigator opinion regarding the relationship of AE to the investigational drug(s).

13.11. Follow-up of Subjects with an Adverse Event

Any AE will be followed to a satisfactory resolution, loss to follow-up, until it becomes stable, or until it can be explained by another known cause(s) (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record.

13.12. Special Procedures for Managing AEs/SAEs

If AEs occur in a subject which are not tolerable, or for which continued administration of investigational drug is not reasonable in view of the potential benefit to subject, the Investigator must decide whether to stop investigational treatment and/or treat the subject. Subject withdrawal should be avoided, if possible. If discontinuation of treatment occurs, every attempt should be made to restart study drug if medically appropriate, whatever the duration of discontinuation.

13.13. Notification of Serious Adverse Events

The Investigator must report all SAEs and pregnancies promptly to Sunovion or its designee, by completing the SAE form and submit by email (or fax) within 24 hours of first becoming aware of the event. Email: sunovionsafety@druginfo.com or Fax: 1-855-278-6344.

The Investigator will be able to contact Dr. Poonam Hundal, the study Medical Monitor, at +1-919-592-1802 or Poonam.Hundal@incresearch.com.

If a SAE is reported via telephone, the Investigator must follow up the initial telephone notification by completing the SAE form and submit by email (or fax).

At the time of the first notification of an SAE, the study site should provide the following information to the Sunovion contact person, if available:

- Subject's study number and initials;
- Subject's date of birth;
- Subject's gender;

- Date of first dose of investigational drug(s);
- Date of last dose of investigational drug(s), if applicable;
- AE term;
- Time and date of occurrence of the event;
- A brief description of the event, outcome to date, and any actions taken;
- The seriousness criteria(on) that were met;
- Concomitant medication at onset of the event;
- Relevant medical history information;
- Relevant laboratory test findings;
- Investigator's opinion of the relationship to investigational drug(s). ("Is there a reasonable possibility that the investigational drug caused the SAE? Yes or No?");
- Whether and when the Investigator was unblinded as to the subject's treatment assignment.

Any missing or additional relevant information concerning the serious (or unexpected) AE should be provided in a written follow-up report.

The Investigator is required to comply with applicable regulations regarding the notification of his/her IRB/REB/IEC.

14. TREATMENTS

14.1. Treatments Administered

APL-130277 sublingual thin film, subcutaneous (s.c.) APO-go® and s.c. APOKYN® will be administered in Period 1, Period 2, and Period 3 in accordance with the randomization scheme. Subjects will receive all three treatment arms at a dose as described in the dosing algorithm, see Table 5. Study medication will be administered in the clinic. Only authorized study site personnel may supply or administer the study medication.

Refer to the Pharmacy Manual (or equivalent) for more details.

14.2. Administration of Study Medication

14.2.1. APL-130277 Product and Administration Procedures

APL-130277 is a near square bilayer film containing apomorphine hydrochloride. APL-130277 is intended for fast sublingual absorption for use in rescue therapy for acute intermittent "OFF" episodes experienced by PD patients. APL-130277 bilayer is composed of 2 layers laminated together: a first layer is composed of cellulose-ether based film, containing drug substance, stabilizers and plasticizers; a second layer contains a pH-modifier (pyridoxine hydrochloride) contained within a similar cellulosic film base, flavor agents and a permeation enhancer. Buffer layer will be on the side of the sublingual film that has an alphanumeric printing.

APL-130277 sublingual thin films will be provided in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg.

Before dosing APL-130277 sublingual thin film, the study staff will read out to subjects:

"The product is a film. It will be placed against the bottom of the tongue. After the dose is placed in the mouth, close your mouth naturally. Let your tongue take a natural position. Do not move the tongue around to try to taste the drug or change its position. Just let it slowly dissolve in place. It will dissolve in 3 to 4 minutes. During that time try not to swallow saliva or the film. When the film is dissolved, raise your hand to let the clinical staff know. We will ask that you open your mouth to show us."

Subjects will be instructed to consume a glass of water immediately prior to dosing, and staff will ensure the sublingual space is free of excess water.

Using gloved hands, or a single-use plastic disposable tweezers, staff will place the product beneath the tongue, with the drug side facing up and placed against the bottom of the tongue (ie, the side of the film that does not have an alphanumeric printing), and ask subjects to close their mouth naturally. Subjects should not swallow the medication and should also try not to swallow their saliva for at least 3 minutes. If, upon inspection at the 3 minute mark, the film is not completely dissolved, subjects should be instructed to close their mouth and hold the study medication under their tongue for another minute (ie, maximum of 4 minutes in total).

If the subject feels the film has fully dissolved prior to the 3 minute mark, they should indicate this to staff by raising their hand, who will then verify. If upon inspection, the film is not completely dissolved, subjects should be instructed to close their mouth again and hold the study

medication under their tongue. Staff may verify at regular intervals, as appropriate, for a duration maximum of 4 minutes in total.

14.2.2. APO-go® Product and Drug Administration Procedures

Subcutaneous apomorphine, APO-go® 30mg/3 mL (10 mg/mL), containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), is supplied as a clear, colorless, sterile, solution in 3 mL cartridges. The 3 mL glass cartridges are used with a manual reusable, multiple dose injector pen.

APO-go® is for subcutaneous injection only.

Prior to dosing, the injection pen will be primed and prepared in accordance with the Summary of Product Characteristics and Patient Information Leaflet (see Section 19.3). The injection will be given in the lower abdomen, thigh or upper arm (left or right depending on the clinical Investigator's judgment) contra-lateral to the arm used to obtain blood samples. The injection site must be the same for both subcutaneous treatments and documented in the source. Prior to injection, the injection site will be cleaned with an alcohol swab and allowed to air dry. When ready for dosing, approximately 1 inch of skin and fat tissue at the injection location will be gently pinched by clinic staff, and the needle inserted. Once dosing is complete, the needle will be removed and subjects will be asked to return to their beds immediately.

14.2.3. APOKYN® Product and Drug Administration Procedures

Subcutaneous apomorphine, APOKYN® 30 mg/3 mL (10 mg/mL), containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), USP is supplied as a clear, colorless, sterile, solution in 3 mL cartridges. The 3 mL glass cartridges are used with a manual reusable, multiple dose injector pen.

APOKYN® is for subcutaneous injection only.

Prior to dosing, the injection pen will be primed and prepared in accordance with the Prescribing Information and Pen Instructions (see Section 19.1 and Section 19.2). The injection will be given in the lower abdomen, thigh or upper arm (left or right depending on the clinical Investigator's judgment) contra-lateral to the arm used to obtain blood samples. The injection site must be the same for both subcutaneous treatments and documented in the source. Prior to injection, the injection site will be cleaned with an alcohol swab and allowed to air dry. When ready for dosing, approximately 1 inch of skin and fat tissue at the injection location will be gently pinched by clinic staff, and the needle inserted. Once dosing is complete, the needle will be removed and subjects will be asked to return to their beds immediately.

14.3. Storage

The Investigator is responsible for ensuring the proper storage of all study medication according to procedures agreed in advance. Each Investigator is required to keep investigational drug product in a locked cabinet or other secure storage contained with limited access to personnel. Temperature logs must be maintained for the storage room.

APL-130277: Unit dose pouches must be stored at controlled room temperature: 68-77°F (20-25°C).

APO-go®: Cartridges will be stored as per the product insert; do not store above 25°C.

APOKYN®: Cartridges will be stored as per the product insert; "Store at 25°C (77°F) Excursions permitted to 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]".

The Investigator must maintain accurate and adequate records including expiry dates, lot number, and quantities received, individual usage, etc. At the end of the study, the Investigator must also return unused supplies to the Sponsor giving an account of usage in a trial whether or not the trial is completed or terminated. At the time of return to the Sponsor, the Investigator must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the Investigator's possession. Certificates of delivery and returns must be signed and filed in the Study Site File.

14.4. Packaging and Labeling

The study medications will be labeled with study specific information meeting all the applicable regulatory requirements.

Individual sublingual thin films of APL-130277 will be packaged in individual unit dose pouches.

14.5. Drug Accountability

Drug supplies, which will be provided by Sunovion or a CRO appointed by Sunovion, must be kept in a secure, limited access storage area.

The Investigator, pharmacist, and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to Sunovion of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the investigational product(s) and trial subjects. The Investigator, pharmacist, and/or investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the clinical trial protocol and reconcile all investigational product(s) received from Sunovion. At the time of return to Sunovion, the Investigator or site designate must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator's possession.

Note: If any of the investigational drug is not dispensed; is lost, stolen, spilled, unusable; or arrives at the clinical site in a damaged container, this information must be documented and reported to Sunovion and appropriate regulatory agencies as required. The investigational product(s) will only be administered to subjects participating in this study. Only authorized study site personnel may supply or administer the investigational product(s).

14.6. Method of Assigning Subjects to Treatment Groups

This three-way crossover study includes 3 treatments, 3 periods and 6 sequences (see Table 4). Subjects will receive all three treatment arms with a minimum 1-day wash-out between each visit (excluding the screening visit).

14.7. Randomization and Blinding

At Screening, the IWRS will assign a unique subject identification number to the subject known as the Screening Number. This number will be associated with the subject throughout the study. Every subject that signs an ICF must be entered into the IWRS regardless of eligibility in order to obtain a Screening Number. This 7-digit number will consist of a 4-digit site ID followed by a 3-digit number assigned sequentially within each site starting at 001.

Following Sponsor approval, subjects will be randomized centrally at a study level after the Screening Visit has been completed to one of the six randomization sequences using the Williams design.

No stratification factors will be used. The randomization scheme will be designed by the study statistician. Once designed, an independent randomization expert will execute the randomization in the IWRS. The randomization number is used to identify the treatment sequence (APL-130277, APO-go®, APOKYN®) of the treatment that will be administered to the subject during the Three-Way Open-Label Randomized Crossover Phase (Period 1, Period 2, Period 3).

A randomization number can only be assigned to one subject and cannot be reused once assigned.

15. STATISTICAL ANALYSES

15.1. Statistical Analysis Plan

Full statistical considerations, table mock-ups and final analysis of safety and efficacy data collected in this study will be outlined in a formal Statistical Analysis Plan (SAP). The SAP will serve as a complement to the study protocol and supersedes it in case of differences.

15.2. Summary of Statistical Methods

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics for categorical data will include frequency counts and percent. The total number of patients in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise, Significance testing will be 2-sided using $\alpha = 0.05$, unless otherwise specified.

15.3. Analysis Populations

15.3.1. Safety Population

All subjects who receive at least one dose of study drug will be included in the safety analysis set. The safety analysis set will be used for the analysis of the safety endpoints and the subjects will be grouped according to the treatment that they received.

15.3.2. Pharmacokinetic Population

The PK analysis set includes all subjects with at least one PK evaluation.

15.4. Sample Size Calculation

With a sample size of 12 subjects, a two-sided 90% confidence interval for the difference in paired PK parameter means on the log scale will have an interval that extends no more than 0.221 units from the observed difference with 90% coverage probability. This calculation assumes a coefficient of variation of 35% for the difference on the original scale. If the observed mean difference on the log scale were zero, this would correspond to a 90% confidence interval for the ratio of geometric means of (80.2%, 124.7%) on the original scale.

15.5. Safety Analysis

Safety and tolerability will be evaluated through summary tables and individual listings of all safety parameters collected in the study.

15.6. Pharmacokinetic Analysis

Pharmacokinetic parameters will be derived using noncompartmental methods employing WinNonlin® Phoenix version 6.3 or higher (Pharsight, St Louis, MO). Pharmacokinetic analysis will be conducted using concentration-time data for apomorphine and metabolites.

Apomorphine concentrations and metabolites (norapomorphine and apomorphine sulphate) will be measured in plasma using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma samples collected for PK analysis may also be used for the additional characterization of putative metabolites of APL-130277 and formulation components, if needed.

For pharmacokinetic analysis concentrations that are below the limit of quantification (BLQ) will be assigned a value of zero when they precede quantifiable samples in the initial portion of the profile. Following C_{max}, BLQ values embedded between two quantifiable data points will be treated as missing when calculating area under the curve. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. When consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

PK parameters (Table 6) will be estimated by noncompartmental methods from plasma samples. Actual elapsed time from dosing will be used to determine all individual PK parameters.

Table 6: Pharmacokinetic Parameters to be Estimated

Parameter	Definition
C_{max}	Maximum plasma concentration (ng/mL), observed by inspection of individual subject plots of plasma concentration versus time.
T_{max}	Time (hr) from dosing to C_{max}, observed by inspection of individual subject plots of plasma concentration versus time.
AUC_{last}	Area under the plasma concentration vs. time curve (hr•ng/mL) from dosing to the last measurable concentration, calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids.
AUC_{∞}	Area under the plasma concentration vs. time curve (hr•ng/mL) from Hour 0.0 to infinity. AUC_{∞} is calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$. The extrapolated $AUC_{t-\infty}$ is estimated as the ratio of the last measurable plasma concentration and the apparent terminal elimination rate constant (C_t/k_{el}). The percentage (%) of AUC_{∞} extrapolated will also be calculated.
λz	Apparent terminal elimination rate constant (hr^{-1}), determined by log-linear regression of the plasma concentration versus time data that was judged to be in the log-linear elimination phase.
$t_{½}$	Apparent terminal elimination half-life (hr), as calculated by the following equation: $t_{½} = 0.693/\lambda_z$.
MRT	Mean residence time (hr) during one dosing interval calculated using the following equation: $MRT = AUMC_{0-\tau}/AUC_{0-\tau}$. $AUMC_{0-\tau}$ is the area under the first moment (time.plasma concentration vs. time) curve.
$F_{T/R}$	The comparative bioavailability calculated as the ratio of the Test/Reference formulation PK parameter (AUC_{last}, AUC_{∞}, C_{max}) uncorrected for dose.
M/P Ratio	Metabolite to Parent exposure ratio (C_{max} and AUC).
CL/F	Apparent total clearance of the drug from plasma after oral administration
V/F	Apparent volume of distribution after non-intravenous administration

The individual subject concentration-time data for apomorphine and metabolites will be listed and displayed graphically on linear and semi-log scales. Plasma apomorphine and metabolite concentration-time data will be summarized descriptively in tabular and graphical formats (linear and semi-log scales) overlaid by dose level. Individual PK parameters from the noncompartmental PK analysis will be tabulated, where calculable, and summarized descriptively. The following summary statistics will be presented for PK parameters: N, arithmetic mean, CV%, SD of the arithmetic mean, median, minimum, maximum, geometric mean and CV% of the geometric mean. T_{max} will be presented as N, median, minimum and maximum.

Figures illustrating the time course of mean drug concentration vs. time for each regimen will be overlaid and presented for relevant comparisons on linear and semi-logarithmic scales, as appropriate. Other analyses such as exploring the relationship between PK parameters and dose will be conducted, as appropriate.

AUC_{last}, AUC_{∞}, C_{max}, T_{max}, $t_{½}$ and λ_z will be evaluated for plasma apomorphine concentrations. Analysis of Variance (ANOVA) will be performed for log-transformed AUC_{last}, AUC_{∞}, and $C_{max.}$ T_{max} will be analyzed using a non-parametric test (Wilcoxon test) while $t_{½}$ will be analyzed using a t-test. Comparative bioavailability will be assessed by estimating the 90% confidence intervals (CI) for the formulation ratios (APL-130277 vs. APO-go® vs. APOKYN®) of geometric means for AUC_{last}, AUC_{∞}, C_{max} and will be calculated based on the ratios of the least squares means and estimates from the ANOVA.

16. STUDY CONDUCT

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study site, review of protocol procedures with the Investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

16.1. Regulations and Guidelines

By signing this study protocol, the Investigator agrees to conduct this study in accordance with all laws, regulations and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the Declaration of Helsinki (including all applicable amendments). While delegation of certain aspects of the study to Sub-Investigators and study coordinators is appropriate, the Principal Investigator (PI) will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The PI is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (eg, Sub-Investigators and study coordinators) and their specific study related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational drugs, and their specific duties within the context of the study. Investigators are responsible for providing Sunovion with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Sunovion and the relevant governing authorities.

See Section 19.4 for additional information.

16.2. Study Initiation

Clinical study staff may not screen or enroll subjects into the study until receiving notification from Sunovion or its designee that the study can be initiated at the clinical site. The clinical site will not be authorized for study initiation until:

- The Sponsor has received the appropriate Regulatory Authority/Agency approval for the protocol and ICF;
- The clinical site has received the appropriate IRB/REB/IEC approval for the protocol and the IRB/REB/IEC-approved ICF;
- The clinical site has a Clinical Trial Agreement in place;
- The clinical site personnel, including the Investigator, have participated in a study initiation meeting.

16.3. Study Documentation

16.3.1. Investigator's Regulatory Documents

The regulatory documents listed below must be received from the Investigator and reviewed and approved by Sunovion or its designee before the clinical site can initiate the study and before Sunovion will authorize shipment of investigational drug to the clinical site. Copies of the Investigator's regulatory documents must be retained at the clinical site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the APL-130277 IB, copies of regulatory references, copies of IRB/REB/IEC correspondence, and investigational drug accountability records must be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

Documents Required for Regulatory Packet:

Confidentiality Agreement	Signed Clinical Trial Agreement
Final Protocol	PI CV
Final Protocol Amendments (if any)	PI Medical License
Protocol Signature Pages	Sub-Investigator CV
Protocol Amendment Signature Pages (if applicable)	Sub-Investigator License PI signed FDA Form 1572
APL-130277 IB	IRB Approvals
Signed Financial Disclosure	IRB Membership List / Assurance Statement
Regulatory Agency Approval	Approved Informed Consent Template(s)

Additional documentation requirements may be communicated by Sunovion staff (or it's designate).

16.3.2. Case Report Forms

If the study is managed using an Electronic Data Capture (EDC) system, the Investigator agrees to maintain accurate CRFs/EDC modules and source documentation as part of the case histories for all subjects who sign an ICF.

CRFs/EDC modules are considered confidential documents and should be handled and stored accordingly. Sunovion or its designee will provide the necessary training on the use of the specific EDC system used during the study to ensure that the information is captured accurately and appropriately.

In order to ensure data accuracy, EDC module data for individual subject visits should be completed as soon as possible following the visit and in accordance with the site Clinical Trial Agreement in place. EDC data will be reviewed by the CRA during monitoring visits. The CRA will verify data recorded with source documents.

All corrections or changes requested to the study data must be made as soon as possible by the study site, and verified by the Investigator. When all incorrect and/or inconsistent data has been accounted for, EDC data will be considered complete. All corrections or changes made to any study data must be appropriately tracked in an audit trail.

When applicable, the site is expected to notify the Study Medical Monitor before breaking the study blind, unless it is in the subject's best interest if the blind is broken immediately.

16.3.3. Source Documents

All information recorded in the CRF must be supported by corresponding source documentation. Examples of acceptable source documentation include but are not limited to hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. If available, source documents for at least the 2 years prior to screening will be reviewed by the CRA to verify the subject's eligibility for the study.

Original versions of the laboratory reports and ECG tracings will be retained at the clinical site with the subject's source documents.

16.4. Data Quality Assurance

Sunovion and its designees will perform quality control and assurance checks on all clinical studies that it sponsors. Sunovion, or its designee, will be responsible for additional data quality assurance related to the clinical data being generated, entered and maintained as part of this clinical study.

16.4.1. Monitoring the Study

Clinical Research Associates (CRAs) will conduct site visits at the study facilities to monitor the study. The Investigator agrees to allow these CRA(s) and other authorized Sunovion personnel access. The clinical site will be monitored by Sunovion and/or it's designate to ensure compliance with the protocol, GCP, and applicable regulations and guidelines. As representatives of Sunovion, CRAs are responsible for following the study protocol closely and notifying project management of any noted deviations. The assigned CRA(s) will visit the Investigator and clinical site at periodic intervals and maintain periodic communication. The CRA(s) will maintain current knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. While on site, the CRA(s) will review regulatory documents, compare entries in the source documents, and review investigational drug accountability records. The CRA will ask for clarification and/or correction of any noted inconsistencies.

By signing the protocol, the Investigator agrees to meet with the CRA during clinical site visits, to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation and medical records, to the clinical supplies dispensing and storage area,

and agrees to assist the monitors in their activities, if requested. The Investigator also agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

16.4.2. Routine Data Collection

CRFs will be reviewed by the CRA during monitoring visits. The CRA will verify data with source documents. If the CRA's comparison of the original CRF data with source documents reveals data discrepancies or omissions that require study staff to make corrections, corrections will be made. After the CRF data have been monitored and all corrections have been made, the Investigator must appropriately document within the data system his/her agreement with the data contained therein. If corrections are required subsequent to the Investigator's signature, the Investigator must document his/her agreement with the CRF data to confirm the accuracy of the changed data. A copy of all CRF data will be retained at the clinical site. If corrections are required after all data have been electronically transferred, corrections that have been made must be verified in writing by the Investigator, and new data provided to Sunovion.

Should an EDC system be implemented, the CRA will verify data with source documents. If the CRA's comparison of the original EDC module data with source documents reveals data discrepancies or omissions that require study staff to make corrections, the corrections will be made as outlined in the Study Monitoring Plan. After the EDC module data have been monitored and all corrections have been made, the Investigator must appropriately document within the data system his/her agreement with the data contained therein. If corrections are required subsequent to the Investigator's signature, the Investigator must document his/her agreement with the EDC module data to confirm the accuracy of the changed data. A copy of all EDC module data will be retained at the clinical site. If corrections are required after all data have been electronically transferred, the corrections must be made as instructed in site training.

16.4.3. Data Management

A vendor contracted by Sunovion will provide the data management system and data management services for the study. An EDC system may be implemented.

Clinical site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to review and document data to ensure the accuracy of the corrected and/or clarified data. If an EDC system is implemented, this documentation will be electronic. Query forms or documentation must be generated and filed by the site.

16.4.4. Study Termination

The study may be terminated at Sunovion's discretion at any time for any reason. If Sunovion discovers conditions that warrant early termination of the study, the Investigator will be notified by Sunovion or its designee. Examples of conditions that may warrant premature termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study; and
- The decision on the part of Sunovion to suspend or discontinue testing, evaluation, or development of the investigational product.

16.4.5. Clinical Site Closure

On termination of the study, all screening and ongoing study related procedures conducted at the clinical site will be closed. Sunovion may terminate participation of the clinical site at any time. Examples of conditions that may warrant premature termination of a clinical site include, but are not limited to the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines;
- Inadequate subject enrollment;
- Administrative reasons.

17. GENERAL CONSIDERATIONS

17.1. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Sunovion. The protocol amendment must be signed by the Investigator and approved by the IRB/REB/IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

17.2. Use of Information and Publication

All information concerning APL-130277, Sunovion's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Sunovion to the Investigator and not previously published, is considered confidential and remains the sole property of Sunovion. The CRFs also remain the property of Sunovion. The Investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Sunovion in connection with the continued development of APL-130277 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of APL-130277 data resulting from this study requires prior review and written approval of Sunovion, which will not be unreasonably withheld. Abstracts, manuscripts, and presentation materials should be provided to Sunovion for review at least 30 days prior to the relevant submission deadline.

After publication of the results of the multi-center study or 24 months after the clinical study report has been finalized, whichever comes first, the Sponsor acknowledges the Investigator's rights to publish results from this study. Any such scientific paper, presentation, communication, or other information concerning the study described in this protocol must be submitted to the Sponsor for review prior to submission for publication/presentation.

17.3. Records Retention

The Investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (1) 2 years after the last marketing authorization for the investigational drug has been approved or Sunovion has discontinued its research with respect to such drug; or (2) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify Sunovion in writing of its intent to destroy all such material. Sunovion shall have 30 days to respond to the Investigator's notice, and Sunovion shall have a further opportunity to retain such materials at Sunovion's expense.

17.4. Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the study team has determined that specimens are no longer needed and the decision has been made

that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

17.5. Subject Injury

In general, specific to provisions in the clinical trial agreement, if a subject is injured as a direct result of a test article and the site, its staff and Investigators have followed the protocol and all documentation supporting the proper running of the trial, Sunovion will pay for reasonable and necessary medical treatment for the injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, Sunovion shall comply with such laws or regulations. Where applicable, Sunovion has taken specific national insurance.

18. REFERENCES

Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord*. 2001;16(3):448-58.

APOMORPHINE treatment for morphine addiction. *Br J Addict Alcohol Other Drugs*. 1949;46(2):93-101.

Corsini GU, Del Zompo M, Gessa GL, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. *Lancet.* 1979;1(8123):954-6.

Cotzias GC, Papavasiliou PS, Fehling C, Kaufman B, Mena I. Similarities between neurologic effects of L-dipa and of apomorphine. *N Engl J Med.* 1970;282(1):31-3.

Hornykiewicz O. Basic research on dopamine in Parkinson's disease and the discovery of the nigrostriatal dopamine pathway: the view of an eyewitness. *Neurodegener Dis.* 2008;5:114–7.

Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. *J Pharmacol Exp Ther.* 2002;303(2):791-804.

Mouradian MM, Heuser IJ, Baronti F, et al. Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol.* 1989;25(5):523-6.

Schwab RS, Amador LV, Lettvin JY. Apomorphine in Parkinson's disease. *Trans Am Neurol Assoc.* 1951;56: 251–3.

Stocchi F, Vacca L, Ruggieri S, et al. Intermittent vs. continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol.* 2005;62(6):905-10.

Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. *Neurol Clin.* 1996;14:317-35.

19. APPENDICES

19.1. APPENDIX I: APOKYN® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APOKYN® safely and effectively. See full prescribing information for APOKYN®.

APOKYN® (apomorphine hydrochloride injection)
For Subcutaneous Use Only
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Premedication and Concomitant Medication (2.2)	03/2017
Warnings and Precautions, Nausea and Vomiting (5.2)	03/2017

----------INDICATIONS AND USAGE----------

APOKYN is a non-ergoline dopamine agonist indicated 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 (1)

----------DOSAGE AND ADMINISTRATION----------

- For subcutaneous use only (2.1)
- Always express APOKYN dose in mL to minimize dosing errors (2.1)
- The starting dose of APOKYN is 0.2 mL (2 mg); give the first dose under medical supervision; titrate the dose to effect and tolerance; the maximum recommended dose is 0.6 mL (2.3)
- Treatment with a concomitant antiemetic, e.g., trimethobenzamide, is recommended, starting 3 days prior to the first dose of APOKYN. Treatment with trimethobenzamide should only be continued as long as necessary to control nausea and vomiting, and generally no longer than two months (2.2, 5.2, 6.1, 17)
- APOKYN doses must be separated by at least 2 hours (2.6)
- Renal impairment: reduce test dose, and reduce starting dose to 0.1 mL (1 mg) (2.4, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Multi-dose glass cartridges, 30 mg/3 mL (10 mg/mL) for use with a multiple-dose pen injector (APOKYN Pen) (3, 16)

----------CONTRAINDICATIONS----------

- Concomitant use of APOKYN with $5HT_3$ antagonists, including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated (4)
- Hypersensitivity to apomorphine, its excipients or sodium metabisulfite (4)

----------WARNINGS AND PRECAUTIONS----------

- For subcutaneous use only; thrombus formation and pulmonary embolism have followed intravenous administration of APOKYN (5.1)
- Falling asleep during activities of daily living, and daytime somnolence may occur (5.3)
- Syncope and hypotension/orthostatic hypotension may occur (5.4, 5.5)
- Falls may occur, or increase (5.6)
- May cause hallucinations and psychotic-like behavior (5.7)
- May cause dyskinesia or exacerbate pre-existing dyskinesia (5.8)
- May cause problems with impulse control and impulsive behaviors (5.9)
- May cause coronary events (5.10)
- May prolong QTc and cause torsades de pointes or sudden death (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence at least 10% greater on APOKYN than on placebo) were yawning, drowsiness/somnolence, dyskinesias, dizziness/postural hypotension, rhinorrhea, nausea and/or vomiting, hallucination/confusion, and edema/swelling of extremities (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-877-727-6596 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Concomitant use of antihypertensive medications and vasodilators: increased risk for hypotension, myocardial infarction, pneumonia, falls, and injuries (7.2)
- Dopamine antagonists such as neuroleptics or metoclopramide, may diminish the effectiveness of APOKYN (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Geriatric Use: In clinical trials, patients 65 years of age and older were more likely to experience certain adverse events (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

---

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APOKYN (apomorphine hydrochloride injection) is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease. APOKYN has been studied as an adjunct to other medications *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

APOKYN is indicated for subcutaneous administration only *[see Warnings and Precautions (5.1)]* and only by a multiple-dose APOKYN Pen with supplied cartridges. The initial dose and dose titrations should be performed by a healthcare provider. Blood pressure and pulse should be measured in the supine and standing position before and after dosing.

A caregiver or patient may administer APOKYN if a healthcare provider determines that it is appropriate. Instruct patients to follow the directions provided in the Patients Instructions For Use. Because the APOKYN Pen has markings in milliliters (mL), the prescribed dose of APOKYN should be expressed in mL to avoid confusion.

Visually inspect the APOKYN drug product through the viewing window for particulate matter and discoloration prior to administration. The solution should not be used if discolored (it should be colorless), or cloudy, or if foreign particles are present. Rotate the injection site and use proper aseptic technique *[see How Supplied/Storage and Handling (16) and Patient Counseling Information (17)]*.

2.2 Premedication and Concomitant Medication

Because of the high incidence of nausea and vomiting with APOKYN treatment, an antiemetic, e.g., trimethobenzamide 300 mg three times a day, should be started 3 days prior to the initial dose of APOKYN *[see Warnings and Precautions (5.2)]*. Treatment with trimethobenzamide should only be continued as long as necessary to control nausea and vomiting, and generally no longer than two months after initiation of treatment with APOKYN, as trimethobenzamide increases the incidence of somnolence, dizziness and falls in patients treated with APOKYN *[see Warnings and Precautions (5.2)]*.

Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with drugs of the $5HT_3$ antagonist class including antiemetics (for example, ondansetron, granisetron, dolasetron, palonosetron) and alosetron are contraindicated *[see Contraindications (4)]*.

2.3 Dosing Information

The recommended starting dose of APOKYN is 0.2 mL (2 mg). Titrate on the basis of effectiveness and tolerance, up to a maximum recommended dose of 0.6 mL (6 mg) *[see Clinical Studies (14)]*.

There is no evidence from controlled trials that doses greater than 0.6 mL (6 mg) gave an increased effect and therefore, individual doses above 0.6 mL (6 mg) are not recommended. The average frequency of dosing in the development program was 3 times per day. There is limited experience with single doses greater than 0.6 mL (6 mg), dosing more than 5 times per day and with total daily doses greater than 2 mL (20 mg).

Begin dosing when patients are in an "off" state. The initial dose should be a 0.2 mL (2 mg) test dose in a setting where medical personnel can closely monitor blood pressure and pulse. Both supine and standing blood pressure and pulse should be checked pre-dose and at 20 minutes, 40 minutes, and 60 minutes post-dose (and after 60 minutes, if there is significant hypotension at 60 minutes). Patients who develop clinically significant orthostatic hypotension in response to this test dose of APOKYN should not be considered candidates for treatment with APOKYN.

If the patient tolerates the 0.2 mL (2 mg) dose, and responds adequately, the starting dose should be 0.2 mL (2 mg), used on an as needed basis to treat recurring "off" episodes. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

The general principle guiding subsequent dosing (described in detail below) is to determine that the patient needs and can tolerate a higher test dose, 0.3 mL or 0.4 mL (3 mg or 4 mg, respectively) under close medical supervision. A trial of outpatient dosing may follow (periodically assessing both efficacy and tolerability), using a dose 0.1 mL (1 mg) lower than the tolerated test dose.

If the patient tolerates the 0.2 mL (2 mg) test dose but does not respond adequately, a dose of 0.4 mL (4 mg) may be administered under medical supervision, at least 2 hours after the initial test dose, at the next observed "off" period. If the patient tolerates and responds to a test dose of 0.4 mL (4 mg), the initial maintenance dose should be 0.3 mL (3 mg) used on an as needed basis to treat recurring "off" episodes as an outpatient. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

If the patient does not tolerate a test dose of 0.4 mL (4 mg), a test dose of 0.3 mL (3 mg) may be administered during a separate "off" period under medical supervision, at least 2 hours after the previous dose. If the patient tolerates the 0.3 mL (3 mg) test dose, the initial maintenance dose should be 0.2 mL (2 mg) used on an as needed basis to treat existing "off" episodes. If needed, and the 0.2 mL (2 mg) dose is tolerated, the dose can be increased to 0.3 mL (3 mg) after a few days. In such a patient, the dose should ordinarily not be increased to 0.4 mL (4 mg) on an outpatient basis.

2.4 Dosing in Patients with Renal Impairment

For patients with mild and moderate renal impairment, the test dose and starting dose should be reduced to 0.1 mL (1 mg) *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

2.5. Dosing in Patients with Hepatic Impairment

Closely monitor patients with mild and moderate hepatic impairment *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.7)]*.

2.6 Re-treatment and Interruption in Therapy

If a single dose of APOKYN is ineffective for a particular "off" period, a second dose should not be given for that "off" episode. The efficacy of the safety of administering a second dose for a single "off" episode has not been studied systematically. Do not administer a repeat dose of APOKYN sooner than 2 hours after the last dose.

Patients who have an interruption in therapy of more than a week should be restarted on a 0.2 mL (2 mg) dose and gradually titrated to effect and tolerability.

3 DOSAGE FORMS AND STRENGTHS

APOKYN 30 mg/3 mL (10 mg/mL) containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), USP is supplied as a clear, colorless, sterile, solution in a 3 mL (30 mg) cartridge. The 3 mL (30 mg) glass cartridge is used with a manual reusable, multiple-dose pen injector

(APOKYN Pen). A single cartridge, pen and needle can deliver doses up to 1 mL (10 mg) in 0.02 mL (0.2 mg) increments. The multiple-dose pen injector is provided in a package with six needles.

4 CONTRAINDICATIONS

APOKYN is contraindicated in patients:

- Using concomitant drugs of the $5HT_3$ antagonist class including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron *[see Drug Interactions (7.1)]*. There have been reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron.

- With hypersensitivity/allergic reaction characterized by urticaria, rash, pruritus, and/or various manifestations of angioedema to apomorphine or to any of the excipients including a sulfite (i.e., sodium metabisulfite). Patients with a sulfite sensitivity may experience various allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic attacks. Patients who experience any hypersensitivity/allergic reaction to APOKYN should avoid taking APOKYN again.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Adverse Reactions After Intravenous Administration

Following intravenous administration of APOKYN, serious adverse reactions including thrombus formation and pulmonary embolism due to intravenous crystallization of apomorphine have occurred. Consequently, APOKYN should not be administered intravenously.

5.2 Nausea and Vomiting

APOKYN causes severe nausea and vomiting when it is administered at recommended doses. Because of this, in domestic clinical studies, 98% of all patients were pre-medicated with trimethobenzamide, an antiemetic, for three days prior to study enrollment, and were then encouraged to continue trimethobenzamide for at least 6 weeks. Even with the use of concomitant trimethobenzamide in clinical studies, 31% and 11% of the APOKYN-treated patients had nausea and vomiting, respectively, and 3% and 2% of the patients discontinued APOKYN due to nausea and vomiting, respectively. Among 522 patients treated, 262 (50%) discontinued trimethobenzamide while continuing APOKYN. The average time to discontinuation of trimethobenzamide was about 2 months (range: 1 day to 33 months). For the 262 patients who discontinued trimethobenzamide, 249 patients continued apomorphine without trimethobenzamide for a duration of follow-up that averaged 1 year (range: 0 years to 3 years).

The effect of trimethobenzamide on reducing nausea and vomiting during treatment with APOKYN was evaluated in a 12-week, placebo-controlled study in 194 patients. The study suggests that trimethobenzamide reduces the incidence of nausea and vomiting during the first 4 weeks of APOKYN treatment (incidence of nausea and vomiting 43% on trimethobenzamide vs. 59% on placebo). However, over the 12-week period, compared with placebo, patients treated with trimethobenzamide had a greater incidence of somnolence (19% for trimethobenzamide vs. 12% for placebo), dizziness (14% for trimethobenzamide vs. 8% for placebo), and falls (8% for trimethobenzamide vs. 1% for placebo). Therefore, the benefit of treatment with trimethobenzamide must be balanced with the risk for those adverse events, and treatment with trimethobenzamide should only be continued as long as necessary to control nausea and vomiting, and generally no longer than two months.

The ability of concomitantly administered antiemetic drugs (other than trimethobenzamide) has not been studied. Antiemetics with anti-dopaminergic actions (e.g., haloperidol, chlorpromazine, promethazine, prochlorperazine, metaclopramide) have the potential to worsen the symptoms in patients with Parkinson's disease and should be avoided.

5.3 Falling Asleep During Activities of Daily Living and Somnolence

There have been reports in the literature of patients treated with APOKYN subcutaneous injections who suddenly fell asleep without prior warning of sleepiness while engaged in activities of daily living. Somnolence is commonly associated with APOKYN, and it is reported that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, even if patients do not give such a history. Somnolence was reported in 35% of patients treated with APOKYN and in none of the patients in the placebo group. Prescribers should reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with APOKYN, advise patients of the risk of drowsiness and ask them about factors that could increase the risk with APOKYN, such as concomitant sedating medications and the presence of sleep disorders. If a patient develops significant daytime sleepiness or falls asleep during activities that require active participation (e.g., conversations, eating, etc.), APOKYN should ordinarily be discontinued. If a decision is made to continue APOKYN, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to determine whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.4 Syncope

In clinical studies, approximately 2% of APOKYN-treated patients experienced syncope.

5.5 Hypotension / Orthostatic Hypotension

Dopamine agonists, including APOKYN, may cause orthostatic hypotension at any time but especially during dose escalation. Patients with Parkinson's disease may also have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk.

Patients undergoing titration of APOKYN showed an increased incidence (from 4% pre-dose to 18% post-dose) of systolic orthostatic hypotension (≥ 20 mmHg decrease) when evaluated at various times after in-office dosing. A small number of patients developed severe systolic orthostatic hypotension (≥ 30 mmHg decrease and systolic BP ≤ 90 mmHg) after subcutaneous apomorphine injection. In clinical trials of APOKYN in patients with advanced Parkinson's disease, 59 of 550 patients (11%) had orthostatic hypotension, hypotension, and/or syncope. These events were considered serious in 4 patients (< 1%) and resulted in withdrawal of APOKYN in 10 patients (2%). These events occurred both with initial dosing and during long-term treatment. Whether or not hypotension contributed to other significant adverse events seen (e.g., falls), is unknown. APOKYN causes dose-related decreases in systolic (SBP) and diastolic blood pressure (DBP) *[see Clinical Pharmacology (12.2)]*.

The hypotensive effects of APOKYN may be increased by the concomitant use of alcohol, antihypertensive medications, and vasodilators (especially nitrates). Patients should avoid alcohol when using APOKYN. Check blood pressure for hypotension and orthostatic hypotension in patients APOKYN with concomitant antihypertensive medications and/or vasodilators *[see Drug Interactions (7.2)]*.

5.6 Falls

Patients with Parkinson's disease (PD) are at risk of falling due to underlying postural instability, possible autonomic instability, and syncope caused by the blood pressure lowering effects of the drugs used to treat PD. Subcutaneous APOKYN might increase the risk of falling by simultaneously lowering blood pressure and altering mobility *[see Clinical Pharmacology (12.2)]*.

In clinical trials, 30% of patients had events that could reasonably be considered falls and about 5% of patients had falls that were considered serious.

5.7 Hallucinations / Psychotic-Like Behavior

In clinical studies, hallucinations were reported by 14% of the APOKYN-treated patients. In one randomized, double-blind, placebo-controlled study, hallucinations or confusion occurred in 10% of patients treated with APOKYN and 0% of patients treated with placebo. Hallucinations resulted in discontinuation of APOKYN in 1% of patients.

Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior after starting or increasing the dose of APOKYN. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations, including paranoid ideation, delusions, hallucinations, confusion, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should ordinarily not be treated with APOKYN because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of APOKYN *[see Drug Interactions (7.3)]*.

5.8 Dyskinesias

APOKYN may cause dyskinesia or exacerbate pre-existing dyskinesia. In clinical studies, dyskinesia or worsening of dyskinesia was reported in 24% of patients. Overall, 2% of APOKYN-treated patients withdrew from studies due to dyskinesias.

5.9 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges and the inability to control these urges while taking one or more of the medications, including APOKYN, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with APOKYN. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking APOKYN.

5.10 Coronary Events

In clinical studies, 4% of patients treated with APOKYN experienced angina, myocardial infarction, cardiac arrest and/or sudden death; some cases of angina and myocardial infarction occurred in close proximity to APOKYN dosing (within 2 hours), while other cases of cardiac arrest and sudden death were observed at times unrelated to dosing. APOKYN has been shown to reduce resting systolic and diastolic blood pressure and may have the potential to exacerbate coronary (and cerebral) ischemia in

patients with known cardiovascular and cerebrovascular disease. If patients develop signs and symptoms of coronary or cerebral ischemia, prescribers should re-evaluate the continued use of APOKYN.

5.11 QTc Prolongation and Potential for Proarrhythmic Effects

There is a small dose related prolongation of QTc interval with doses of APOKYN greater than 6 mg *[See Clinical Pharmacology (12.2)]*. Doses greater than 6 mg do not provide additional clinical benefit and are not recommended.

Drugs that prolong the QTc interval have been associated with torsades de pointes and sudden death. The relationship of QTc prolongation to torsades de pointes is clearest for larger increases (20 msec and greater), but it is possible that smaller QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, bradycardia, concomitant use of other drugs that prolong the QTc interval, or genetic predisposition (e.g., congenital prolongation of the QT interval). Although torsades de pointes has not been observed in association with the use of APOKYN at recommended doses in clinical studies, experience is too limited to rule out an increased risk. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes.

The risks and benefits of APOKYN treatment should be considered prior to initiating treatment with APOKYN in patients with risk factors for prolonged QTc.

5.12 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

5.13 Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using APOKYN for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

5.14 Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse reactions are believed to be related to the ergoline structure of these dopamine agonists, whether other, nonergot derived dopamine agonists, such as APOKYN, can cause these reactions is unknown.

5.15 Priapism

APOKYN may cause prolonged painful erections in some patients. In clinical studies, painful erections were reported by 3 of 361 APOKYN-treated men, and one patient withdrew from APOKYN therapy because of priapism. Although no patients in the clinical studies required surgical intervention, severe priapism may require surgical intervention.

5.16 Retinal Pathology in Albino Rats

In a 2-year carcinogenicity study of apomorphine in albino rat, retinal atrophy was detected at all subcutaneous doses tested (up to 0.8 mg/kg/day or 2 mg/kg/day in males or females, respectively; less than the maximum recommended human dose of 20 mg/day on a body surface area [mg/m^2] basis). Retinal atrophy/degeneration has been observed in albino rats treated with other dopamine agonists for prolonged periods (generally during 2-year carcinogenicity studies). Retinal findings were not observed in a 39-week subcutaneous toxicity study of apomorphine in monkey at doses up to 1.5 mg/kg/day, a dose similar to the MRHD on a mg/m^2 basis. The clinical significance of the finding in rat has not been established but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling:

- Nausea and Vomiting *[see Warnings and Precautions (5.2)]*
- Syncope *[see Warnings and Precautions (5.4)]*
- Hypotension/Orthostatic Hypotension *[see Warnings and Precautions (5.5)]*
- Falls *[see Warnings and Precautions (5.6)]*
- Hallucinations/Psychotic-Like Behavior *[see Warnings and Precautions (5.7)]*
- Dyskinesias *[see Warnings and Precautions (5.8)]*
- Coronary Events *[see Warnings and Precautions (5.10)]*
- Priapism *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions (number of unique patients experiencing an adverse reaction associated with treatment per total number of patients treated) observed in the clinical trials of a drug cannot be directly compared to the incidence of adverse reactions in the clinical trials of another drug and may not reflect the incidence of adverse reactions observed in practice.

In placebo-controlled trials, most patients received only one subcutaneous dose of APOKYN. All patients received concomitant levodopa and 86% received a concomitant dopamine agonist. All patients had some degree of spontaneously occurring periods of hypomobility ("off episodes") at baseline.

The most common adverse reactions (APOKYN incidence at least 10% greater than placebo incidence) observed in a placebo-controlled trial were yawning, drowsiness/somnolence, dyskinesias, dizziness/postural hypotension, rhinorrhea, nausea and/or vomiting, hallucination/confusion, and edema/swelling of extremities.

Table 1 presents the most common adverse reactions reported by APOKYN-naïve Parkinson's disease patients who were enrolled in a randomized placebo-controlled, parallel group trial and who were treated for up to 4 weeks (Study 1) *[see Clinical Studies (14)]*. Individual APOKYN doses in this trial ranged from 2 mg to 10 mg, and were titrated to achieve tolerability and control of symptoms.

Table 1: Adverse Reactions Occurring in Two or More APOKYN-Treated Patients in Study 1

	APOKYN (n = 20)	**PLACEBO** (n = 9)
	%	%
Yawning	40	0
Dyskinesias	35	11
Drowsiness or Somnolence	35	0
Nausea and/or Vomiting	30	11
Dizziness or Postural Hypotension	20	0
Rhinorrhea	20	0
Chest Pain/Pressure/Angina	15	11
Hallucination or Confusion	10	0
Edema/Swelling of Extremities	10	0

Other Adverse Reactions

Injection Site Reactions
Patients treated with APOKYN subcutaneous injections during clinical studies, 26% of patients had injection site reactions, including bruising (16%), granuloma (4%), and pruritus (2%).

In addition to those in Table 1, the most common adverse reactions in pooled APOKYN trials (occurring in at least 5% of the patients) in descending order were injection site reaction, fall, arthralgia, insomnia, headache, depression, urinary tract infection, anxiety, congestive heart failure, limb pain, back pain, Parkinson's disease aggravated, pneumonia, confusion, sweating increased, dyspnea, fatigue, ecchymosis, constipation, diarrhea, weakness, and dehydration.

7 DRUG INTERACTIONS

7.1 $5HT_3$ Antagonists
Based on reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron, the concomitant use of APOKYN with $5HT_3$ antagonists including antiemetics (for example, ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated.

7.2 Antihypertensive Medications and Vasodilators
The following adverse events were experienced more commonly in patients receiving concomitant antihypertensive medications or vasodilators (n = 94) compared to patients not receiving these concomitant drugs (n = 456): hypotension 10% vs 4%, myocardial infarction 3% vs 1%, serious pneumonia 5% vs 3%, serious falls 9% vs 3%, and bone and joint injuries 6% vs 2%. The mechanism underlying many of these events is unknown, but may represent increased hypotension *[see Warnings and Precautions (5.5, 5.6)]*.

7.3 Dopamine Antagonists
Since APOKYN is a dopamine agonist, it is possible that concomitant use of dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of APOKYN. Patients with major psychotic disorders, treated with neuroleptics, should be treated with dopamine agonists only if the potential benefits outweigh the risks.

7.4 Drugs Prolonging the QT/QTc Interval
Caution should be exercised when prescribing APOKYN concomitantly with drugs that prolong the QT/QTc interval *[see Warnings and Precautions (5.11)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with use of APOKYN in pregnant women. In animal reproduction studies, apomorphine had adverse developmental effects in rats (increased neonatal deaths) and rabbits (increased incidence of malformation) when administered during pregnancy at clinically relevant doses. These doses were also associated with maternal toxicity *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

No adverse developmental effects were observed when apomorphine (0.3, 1, or 3 mg/kg/day) was administered by subcutaneous injection to pregnant rats throughout organogenesis; the highest dose tested is 1.5 times the maximum recommended human dose (MRHD) of 20 mg/day on a mg/m^2 basis. Administration of apomorphine (0.3, 1, or 3 mg/kg/day) by subcutaneous injection to pregnant rabbits throughout organogenesis resulted in an increased incidence of malformations of the heart and/or great vessels at the mid and high doses; maternal toxicity was observed at the highest dose tested. The no-effect dose for adverse developmental effects is less than the MRHD on a mg/m^2 basis.

Apomorphine (0.3, 1, or 3 mg/kg/day), administered by subcutaneous injection to females throughout gestation and lactation, resulted in increased offspring mortality at the highest dose tested, which was associated with maternal toxicity. There were no effects on developmental parameters or reproductive performance in surviving offspring. The no-effect dose for developmental toxicity (1 mg/kg/day) is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of apomorphine in human milk, the effects of apomorphine on the breastfed infant, or the effects of apomorphine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for APOKYN and any potential adverse effects on the breastfed infant from APOKYN or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the APOKYN clinical development program, there were 239 patients less than age 65 treated with APOKYN and 311 patients who were age 65 years of age or older. Confusion and hallucinations were reported more frequently with patients age 65 and older compared to patients with less than age 65. Serious adverse reactions (life-threatening events or events resulting in hospitalization and/or increased disability) were also more common in patients age 65 and older. Patients age 65 and older were more likely to fall (experiencing bone and joint injuries), have cardiovascular events, develop respiratory disorders, and have gastrointestinal events. Patients age 65 and above were also more likely to discontinue APOKYN treatment as a result of one or more adverse reactions.

8.6 Renal Impairment

The starting APOKYN dose should be reduced in patients with mild or moderate renal impairment because the concentration and exposure (C_{max} and AUC) are increased in these patients. Studies in subjects with severe renal impairment have not been conducted *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Caution should be exercised when administrating APOKYN to patients with mild and moderate hepatic impairment due to the increased C_{max} and AUC in these patients. Studies of subjects with severe hepatic impairment have not been conducted *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In premarketing clinical experience, APOKYN did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse of medications containing APOKYN or levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.

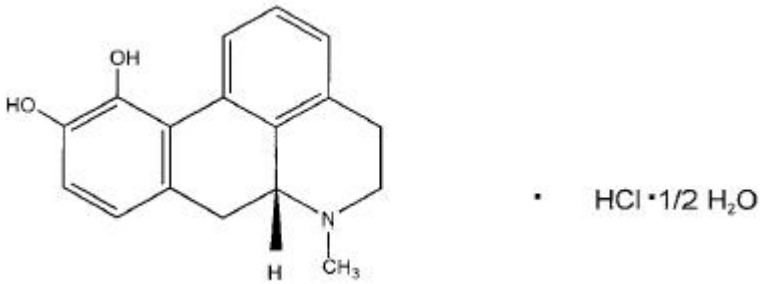
10 OVERDOSAGE

A 62-year-old man accidentally injected 25 mg of APOKYN subcutaneously. After 3 minutes, the patient felt nauseated and lost consciousness for 20 minutes. Afterwards, he was alert with a heart rate 40/minute and a supine blood pressure of 90/50. He recovered completely within an hour.

11 DESCRIPTION

APOKYN (apomorphine hydrochloride injection) contains apomorphine hydrochloride, a non-ergoline dopamine agonist. Apomorphine hydrochloride is chemically designated as 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate with a molecular formula of $C_{17}H_{17}NO_2 \bullet HCL \bullet ½ H_2O$. Its structural formula and molecular weight are:

Figure 1: Structural Formula and Molecular Weight of Apomorphine



M.W. 312.79

Apomorphine hydrochloride appears as minute, white or grayish-white glistening crystals or as white powder that is soluble in water at 80°C.

APOKYN is a clear, colorless, sterile solution for subcutaneous injection and is available in 3 mL (30 mg) multi-dose cartridges. Each mL of solution contains 10 mg of apomorphine hydrochloride, USP as apomorphine hydrochloride hemihydrate, 1 mg of sodium metabisulfite, NF and 5 mg of benzyl alcohol, NF (preservative) in water for injection, USP. In addition, each mL of solution may contain sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the pH of the solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

APOKYN 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.

12.2 Pharmacodynamics

Prolongation of the QTc Interval: In a placebo-controlled study in which patients received increasing single doses of APOKYN from 2 mg to up to 10 mg, the mean difference in QTc (measured by Holter monitor) between APOKYN and placebo was 0 msec at 4 mg, 1 msec at 6 mg, and 7 msec at 8 mg. Too few patients received a 10 mg dose to be able to adequately characterize the change in QTc interval at that dose.

In a controlled trial in which patients were administered placebo or a single dose of APOKYN (mean dose of 5.2 mg; range of 2 mg to 10 mg), the mean difference between APOKYN and placebo in the change in QTc was about 3 msec at 20 minutes and 90 minutes. In the entire database, 2 patients (one at 2 mg and 6 mg, one at 6 mg) exhibited large QTc increments (> 60 msecs from pre-dose) and had QTc intervals greater than 500 msecs acutely after dosing. Doses of 6 mg or less thus are associated with minimal increases in QTc.

Decreases in blood pressure

Dose-dependent mean decrements in systolic blood pressure ranged from 5 mmHg after 2 mg to 16 mmHg after 10 mg. Dose-dependent mean decrements in diastolic blood pressure ranged from 3 mmHg after 2 mg to 8 mmHg after 10 mg. These changes were observed at 20 minutes, and were maximal between 20 and 40 minutes after dosing. Lesser, but still noteworthy blood pressure decrements persisted up to at least 90 minutes after dosing.

12.3 Pharmacokinetics

Absorption

Apomorphine hydrochloride is a lipophilic compound that is rapidly absorbed (time to peak concentration ranges from 10 minutes to 60 minutes) following subcutaneous administration into the abdominal wall. After subcutaneous administration, apomorphine appears to have bioavailability equal to that of an intravenous administration. Apomorphine exhibits linear pharmacokinetics over a dose range of 2 mg to 8 mg following a single subcutaneous injection of APOKYN into the abdominal wall in patients with idiopathic Parkinson's disease.

Distribution

The plasma-to-whole blood apomorphine concentration ratio is equal to one. Mean (range) apparent volume of distribution was 218 L (123 L to 404 L). Maximum concentrations in cerebrospinal fluid (CSF) are less than 10% of maximum plasma concentrations and occur 10 minutes to 20 minutes later.

Metabolism and Elimination

The mean apparent clearance (range) is 223 L/hr (125 L/hr to 401 L/hr) and the mean terminal elimination half-life is about 40 minutes (range about 30 minutes to 60 minutes).

The route of metabolism in humans is not known. Potential routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation. In vitro, apomorphine undergoes rapid autooxidation.

Special Populations
The clearance of apomorphine does not appear to be influenced by age, gender, weight, duration of Parkinson's disease, levodopa dose or duration of therapy.

Renal Impairment
In a study comparing renally-impaired subjects (moderately impaired as determined by estimated creatinine clearance) to healthy matched volunteers, the AUC_0-∞ and Cmax values were increased by approximately 16% and 50%, respectively, following a single subcutaneous administration of APOKYN into the abdominal wall. The mean time to peak concentrations and the mean terminal half-life of apomorphine were unaffected by the renal status of the individual. Studies in subjects with severe renal impairment have not been conducted. The starting dose for patients with mild or moderate renal impairment should be reduced *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Hepatic Impairment
In a study comparing subjects with hepatic impairment (moderately impaired as determined by the Child-Pugh classification method) to healthy matched volunteers, the AUC_0-∞ and C_{max} values were increased by approximately 10% and 25%, respectively, following a single subcutaneous administration of APOKYN into the abdominal wall. Studies in subjects with severe hepatic impairment have not been conducted *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Drug-Drug Interactions
Carbidopa/levodopa: Levodopa pharmacokinetics were unchanged when subcutaneous APOKYN and levodopa were co-administrated in patients. However, motor response differences were significant. The threshold levodopa concentration necessary for an improved motor response was reduced significantly, leading to an increased duration of effect without a change in the maximal response to levodopa therapy.

Other Drugs Eliminated Via Hepatic Metabolism
Based upon an *in vitro* study, cytochrome P450 enzymes play a minor role in the metabolism of apomorphine. *In vitro* studies have also demonstrated that drug interactions are unlikely due to apomorphine acting as a substrate, an inhibitor, or an inducer of cytochrome P450 enzymes.

COMT Interactions
A pharmacokinetic interaction of APOKYN with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since apomorphine appears not to be metabolized by COMT.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Lifetime carcinogenicity studies of apomorphine were conducted in male (0.1, 0.3, or 0.8 mg/kg/day) and female (0.3, 0.8, or 2 mg/kg/day) rats. Apomorphine was administered by subcutaneous injection for 22 months or 23 months, respectively. In males, there was an increase in Leydig cell tumors at the highest dose tested, which is less than the MRHD (20 mg) on a mg/m^2 basis. This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell tumors in rats are not relevant to humans. No drug-related tumors were observed in females; the highest dose tested is similar to the MRHD on a mg/m^2 basis.

In a 26-week carcinogenicity study in P53-knockout transgenic mice, there was no evidence of carcinogenic potential when apomorphine was administered by subcutaneous injection at doses up to 20 mg/kg/day (male) or 40 mg/kg/day (female).

Mutagenesis
Apomorphine was mutagenic in the *in vitro* bacterial reverse mutation (Ames) and the *in vitro* mouse lymphoma *tk* assays. Apomorphine was clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes and in the *in vitro* mouse lymphoma *tk* assay. Apomorphine was negative in the *in vivo* micronucleus assay in mice.

Impairment of Fertility
Apomorphine was administered subcutaneously at doses up to 3 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) to male and female rats prior to and throughout the mating period and continuing in females through gestation day 6. There was no evidence of adverse effects on fertility or on early fetal viability. A significant decrease in testis weight was observed in a 39-week study in cynomolgus monkey at all subcutaneous dose tested (0.3, 1, or 1.5 mg/kg/day); the lowest dose tested is less than the MRHD on a mg/m^2 basis.

In a published fertility study, apomorphine was administered to male rats at subcutaneous doses of 0.2, 0.8, or 2 mg/kg prior to and throughout the mating period. Fertility was reduced at the highest dose tested.

14 CLINICAL STUDIES

The effectiveness of APOKYN in the acute symptomatic treatment of the recurring episodes of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes), in patients with advanced Parkinson's disease was established in three randomized, controlled trials of APOKYN given subcutaneously (Studies 1, 2, and 3). At baseline in these trials, the mean duration of Parkinson's disease was approximately 11 years. Whereas all patients were using concomitant L-dopa at baseline, 86% of patients were using a concomitant oral dopaminergic agonist, 31% were using a concomitant catechol-ortho-methyl transferase (COMT) inhibitor, and 10% were using a concomitant monoamine B oxidase inhibitor. Study 1 was conducted in patients who did not have prior exposure to APOKYN (i.e., APOKYN naïve) and Studies 2 and 3 were conducted in patients with at least 3 months of APOKYN use immediately prior to study enrollment. Almost all patients without prior exposure to APOKYN began taking an antiemetic (trimethobenzamide) three days prior to starting APOKYN and 50% of patients were able to discontinue the concomitant antiemetic, on average 2 months after initiating APOKYN.

The change from baseline in Part III (Motor Examination) of the Unified Parkinson's Disease Rating Scale (UPDRS) served as the primary outcome assessment measure in each study. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability, etc.) in patients with Parkinson's disease.

<u>Study 1</u>
Study 1 was a randomized, double-blind, placebo-controlled, parallel-group trial in 29 patients with advanced Parkinson's disease who had at least 2 hours of "off" time per day despite an optimized oral regimen for Parkinson's disease including levodopa and an oral dopaminergic agonist. Patients with atypical Parkinson's disease, psychosis, dementia, hypotension, or those taking dopamine antagonists were excluded from participation. In an office setting, hypomobility was allowed to occur by withholding the patients' Parkinson's disease medications overnight. The following morning, patients (in a hypomobile state) were started on study treatment in a 2:1 ratio (2 mg of APOKYN or placebo given subcutaneously). At least 2 hours after the first dose, patients were given additional doses of

study medication until they achieved a "therapeutic response" (defined as a response similar to the patient's response to their usual dose of levodopa) or until 10 mg of APOKYN or placebo equivalent was given. At each injection re-dosing, the study drug dose was increased in 2 mg increments up to 4 mg, 6 mg, 8 mg, 10 mg of APOKYN) or placebo equivalent.

Of the 20 patients randomized to APOKYN, 18 achieved a "therapeutic response" at about 20 minutes. The mean APOKYN dose was 5.4 mg (3 patients on 2 mg, 7 patients on 4 mg, 5 patients on 6 mg, 3 patients on 8 mg, and 2 patients on 10 mg). In contrast, of the 9 placebo-treated patients, none reached a "therapeutic response." The mean change-from-baseline for UPDRS Part III score for APOKYN group (highest dose) was statistically significant compared to that for the placebo group (Table 2).

Table 2: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 1

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo	36.3	- 0.1	NA
APOKYN	39.7	- 23.9	- 23.8

Study 2

Study 2 used a randomized, placebo-controlled crossover design of 17 patients with Parkinson's disease who had been using APOKYN for at least 3 months. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received either a single dose of subcutaneous APOKYN (at their usual dose) and placebo on different days in random order. UPDRS Part III scores were evaluated over time. The mean dose of APOKYN was 4 mg (2 patients on 2 mg, 9 patients on 3 mg, 2 patients on 4 mg, and 1 patient each on 4.5 mg, 5 mg, 8 mg, and 10 mg). The mean change-from-baseline UPDRS Part III score for the APOKYN group was statistically significant compared to that for the placebo group (Table 3).

Table 3: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 2

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo	40.1	- 3.0	NA
APOKYN	41.3	- 20.0	- 17.0

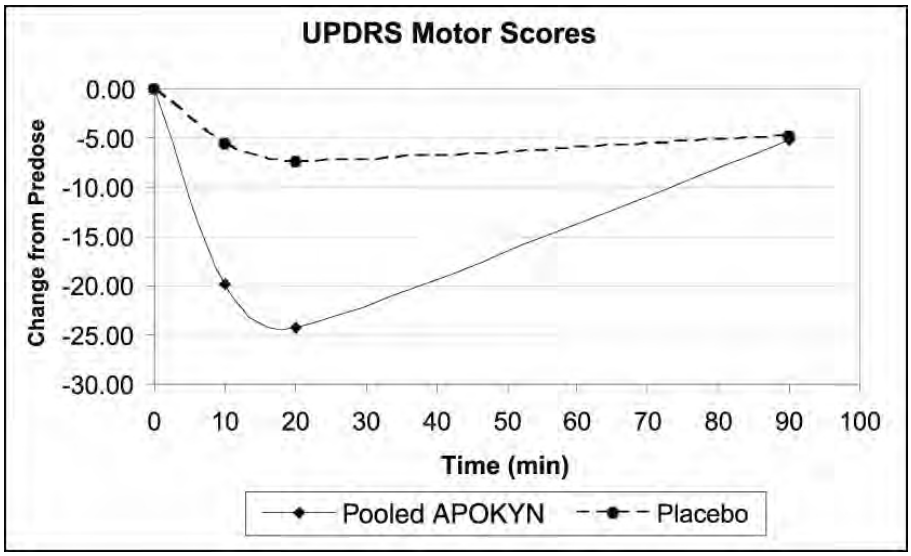
Study 3

Study 3 used a randomized withdrawal design in 4 parallel groups from 62 patients (APOKYN-35; Placebo-27) with Parkinson's disease who had been using APOKYN for at least 3 months. Patients were randomized to one of the following 4 treatments dosed once by subcutaneous administration: APOKYN at the usual dose (mean dose 4.6 mg), placebo at a volume matching the usual APOKYN dose, APOKYN at the usual dose + 2 mg (0.2 mL) (mean dose 5.8 mg), or placebo at a volume matching the usual APOKYN dose + 0.2 mL. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received the randomized treatment. APOKYN doses ranged between 2 mg – 10 mg. The mean change-from-baseline for the APOKYN group for UPDRS Part III scores at 20 minutes post dosing was statistically significant compared to that for the placebo group (Table 4). Figure 2 describes the mean change from baseline in UPDRS Motor Scores over time for pooled APOKYN and placebo administration.

Table 4: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 4

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo (Pooled)	40.6	- 7.4	NA
APOKYN (Pooled)	42.0	- 24.2	- 16.8

Figure 2: Mean Change from Baseline in UPDRS Motor Scores of Pooled APOKYN Groups and Placebo Group in Study 3



In Study 3, the mean changes-from-baseline for UPDRS Part III scores at 20 minutes post dosing for the APOKYN and higher dose APOKYN groups were 24 and 25, respectively. This result suggests that patients chronically treated at a dose of 4 mg might derive little additional benefit from a dose increment of 2 mg. There was also an increased incidence of adverse reactions in patients randomized to higher APOKYN dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

APOKYN is supplied as a 10 mg/mL clear, colorless, sterile, solution in 3 mL (30 mg) glass cartridges.

NDC 27505-004-05
Cartons of five 3 mL cartridges

APOKYN Pen
The pen injector is provided in a package with six needles and a carrying case.

Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Administration with the APOKYN Pen

Instruct patients and caregivers to read the "APOKYN Pen Instructions for Use" and Patient Information. Instruct patients to use APOKYN only as prescribed *[See Dosage and Administration (2)]*.

Instruct patients and caregivers that the APOKYN Pen is dosed in milliliters, not milligrams.

Inform patients and caregivers that it is possible to dial in their usual dose of APOKYN even though the cartridge may contain less than that amount of drug. In this case, they will receive only a partial dose with the injection, and the amount left to inject will appear in the dosing window. To complete the correct dose, patients/caregivers will need to "re-arm" the device and dial in the correct amount of the remaining dose. Patients and caregivers should be alerted to the fact that there may be insufficient drug left in the cartridge to deliver a complete dose (for example, patients and caregivers should be urged to keep records of how many doses they have delivered for each cartridge, so that they can replace any cartridge that has an inadequate amount of drug remaining).

Instruct patients to rotate the injection site and to observe proper aseptic technique.

Advise patients that APOKYN is intended only for subcutaneous injection and must not be given intravenously because of the risk of serious complications such as thrombus formation and pulmonary embolism due to crystallization *[see Warnings and Precautions (5.1)]*.

Avoidance of Concomitant Antiemetic Drugs of $5HT_3$ Antagonist Class

Advise patients that they should not use concomitant drugs of the $5HT_3$ antagonist class including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron with APOKYN. Use of APOKYN with concomitant antiemetic drugs of the $5HT_3$ antagonist class is contraindicated because there have been reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron *[see Contraindications (4)]*.

Hypersensitivity / Allergic Reactions

Advise patients that hypersensitivity/allergic reaction characterized by urticaria, rash, pruritus, and/or various manifestations of angioedema may occur because of APOKYN or any of its excipients including a sulfite (i.e., sodium metabisulfite). Inform patients with a sulfite sensitivity that they may experience various allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic attacks. Advise patients who experience any hypersensitivity/allergic reaction to APOKYN that they should avoid taking APOKYN again *[see Contraindications (4)]*.

Nausea and Vomiting

Advise patients that they may experience severe nausea and/or vomiting and that they should begin taking trimethobenzamide 300 mg orally 3 times per day for 3 days prior to starting APOKYN injections. Advise patients that APOKYN taken with trimethobenzamide may increase the risks for somnolence, dizziness, and falls. Inform patients that their healthcare provider will tell them when trimethobenzamide can be discontinued *[see Warnings and Precautions (5.2)]*.

Falling Asleep Suddenly and Sedation / Sleepiness

Alert patients to the potential sedating effects of APOKYN, including somnolence and falling asleep while engaged in activities of daily living. Instruct patients not to drive a car or engage in other

potentially dangerous activities until they have gained sufficient experience with APOKYN to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) occur, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects of alcohol use, advise patients to limit their alcohol intake *[see Warnings and Precautions (5.3)]*.

Syncope

Advise patients that APOKYN may cause syncope *[see Warnings and Precautions (5.4)]*.

Hypotension / Orthostatic Hypotension

Advise patients that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after months of treatment). Instruct patients to rise slowly after sitting or lying down after taking APOKYN. Instruct patients to limit their alcohol intake because it may potentiate the hypotensive effect of APOKYN *[see Warnings and Precautions (5.5)]*.

Falls

Alert patients that they may have increased risk for falling when using APOKYN *[see Warnings and Precautions (5.6)]*.

Hallucinations and/or Psychotic-Like Behavior

Inform patients that hallucinations or other manifestations of psychotic-like behavior can occur. Tell patients if they have a major psychotic disorder, ordinarily they should not use APOKYN because of the risk of exacerbating the psychosis. Patients with a major psychotic disorder should also be aware that many treatments for psychosis may decrease the effectiveness of APOKYN *[see Warnings and Precautions (5.7)]*.

Dyskinesia

Inform patients that APOKYN may cause and/or exacerbate pre-existing dyskinesias *[see Warnings and Precautions (5.8)]*.

Impulse Control / Compulsive Behaviors

Patients and their caregivers should be alerted to the possibility that they may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges, binge eating and/or other intense urges and the inability to control these urges while taking APOKYN *[see Warnings and Precautions (5.9)]*.

Coronary Events

Inform patients that APOKYN may cause coronary events including angina and myocardial infarction and these outcomes could possibly be related to significant hypotension/orthostatic hypotension *[see Warnings and Precautions (5.10)]*.

QTc Prolongation and Potential for Proarrhythmic Effects

Alert patients that APOKYN may cause QTc prolongation and might produce proarrhythmic effects that could cause torsades de pointes and sudden death. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes *[see Warnings and Precautions (5.11)]*.

Withdrawal-Emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider if they wish to discontinue APOKYN or decrease the dose of APOKYN *[see Warnings and Precautions (5.12)]*.

Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to have a qualified healthcare provider examine that patient's skin periodically for melanomas on a regular basis when using APOKYN *[see Warnings and Precautions (5.13)]*.

Priapism

Advise patients that APOKYN may cause prolonged painful erections and that if this occurs that they should seek medical attention immediately *[see Warnings and Precautions (5.15)]*.

Injection Site Reactions

Inform patients that injections of APOKYN may result in injection site reactions including bruising, granuloma, and pruritus *[see Adverse Reactions (6.1)]*.

Distributed by:

US WorldMeds, LLC
4441 Springdale Rd
Louisville, KY 40241

US WorldMeds, LLC is the exclusive licensee and distributor of APOKYN in the United States and Its territories.

19.2. APPENDIX II: APOKYN® Pen Instructions

APOKYN® Pen Instructions for Use

Designed to be used only with
3 mL APOKYN® (apomorphine hydrochloride injection) Cartridges

For more information, call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).

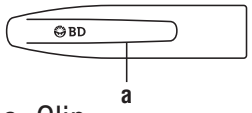
US WorldMeds

APOKYN®
(apomorphine hydrochloride injection)

APOKYN Pen

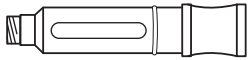
- **APOKYN® (apomorphine hydrochloride injection) is for under the skin (subcutaneous) injection only.**
- **Do not** inject APOKYN into a vein.
- **Do not** use the APOKYN® Pen unless you and your care partner have been taught the right way to use it and both of you understand all of the instructions.
- The **APOKYN Pen** is for use only with 3 mL **APOKYN®** (apomorphine hydrochloride injection) Cartridges.
- The **APOKYN Pen** is only for use by 1 patient and should not be shared.

Gray Pen Cap

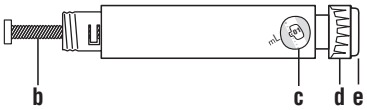


a. Clip

Teal Cartridge Holder

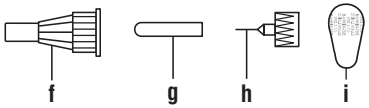


Gray Pen Body



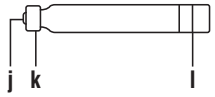
b. Black Rod
c. White Dose Window
d. White Dose Knob
e. Teal Injection Button

Pen Needle Unit



f. Outer Needle Shield
g. Pink Inner Needle Shield
h. Pen Needle
i. Pink Paper Tab

Cartridge



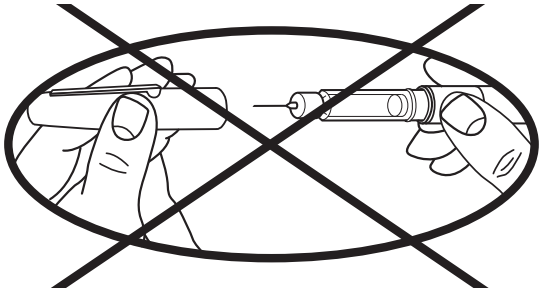
j. Rubber Septum
k. Metal Cap
l. Cartridge Plunger

Read First: Important Safety Information

- The **APOKYN Pen** is a medicine delivery device. It is very important that you or your care partner read this Instructions for Use and follow the instructions for using the **APOKYN Pen** correctly to receive the correct APOKYN dose.
- Always perform a flow check (prime) before every injection and after loading a new cartridge.
- The liquid in the **APOKYN Cartridge** can cause irritation if it gets on your skin or in your eyes. Flush your eyes with cold water and wash the liquid off your skin right away if this happens.

- The BD pen needle unit is sterile. Avoid contaminating the needle after opening. **Do not** place it on a surface or touch other items with the needle.
- **Do not** dial the dose or try to correct a dialing error with the pen needle in the skin. You could receive the wrong dose.
- Be careful when removing the needle. Accidental needle sticks can transmit serious infections.

Never store or carry the APOKYN Pen with a pen needle attached.



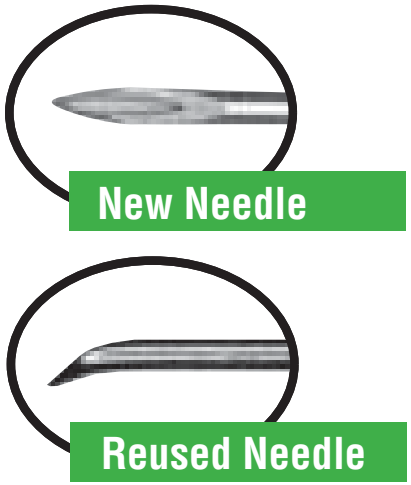
Never recap pen with needle attached.

Storing or carrying the **APOKYN Pen** with a pen needle attached may let:

- Air enter the cartridge
- Medicine leak out

This can affect your APOKYN dose.

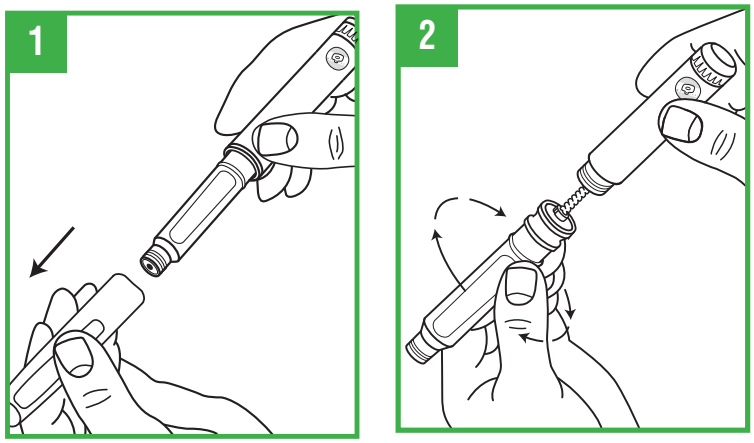
The **APOKYN Pen** should only be used with pen needles (29G x 1/2"). These needles are available through your specialty pharmacy provider or your local pharmacy.



Magnification: 50x

You must use a new, sterile BD pen needle with each injection.

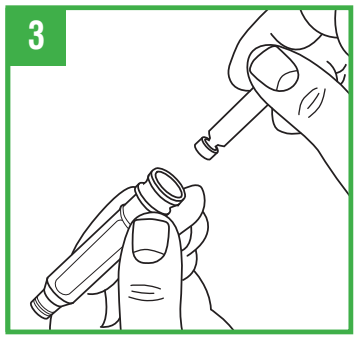
How to Use the APOKYN Pen

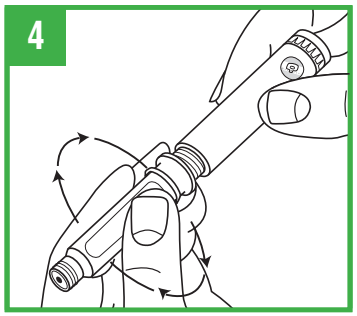


Preparing the APOKYN Pen for Cartridge Loading

Step 1. Remove the gray pen cap by pulling it straight off.

Step 2. Unscrew the teal cartridge holder from the gray pen body by turning it clockwise.

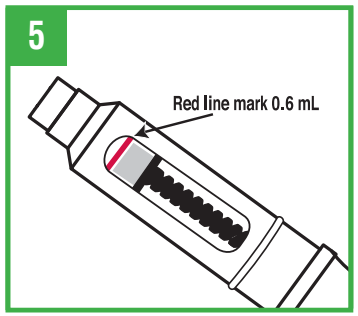




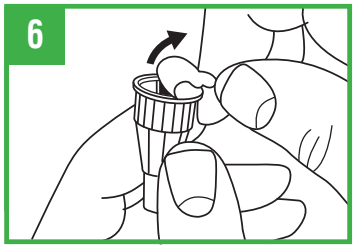
Loading a Cartridge

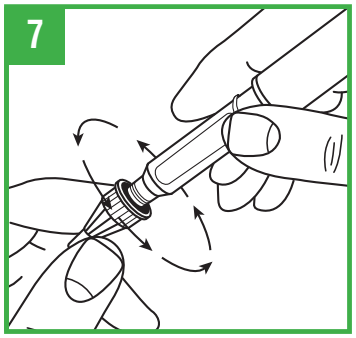
Step 3. Only use **APOKYN** that is clear and colorless. Do not use an **APOKYN Cartridge** that contains medicine that is cloudy, green, or contains particles. Call your specialty pharmacy provider for replacement cartridges. Insert the **APOKYN Cartridge,** metal cap first, into the teal cartridge holder.

Step 4. Lower the gray pen body onto the teal cartridge holder so that the black rod presses against the cartridge plunger. Screw the teal cartridge holder onto the gray pen body. Tighten the pieces by turning the teal cartridge holder clockwise until no gap remains and 1 of the white arrows line up with the white marker on the gray pen body.



Step 5. If you already have a cartridge in the pen and have used the pen, you should check the cartridge through the window in the teal cartridge holder to make sure there is enough **APOKYN** solution in the cartridge to provide your next dose. If the gray cartridge plunger has reached the red line on the cartridge, remove the cartridge and insert a new cartridge into the pen before attaching the pen needle and preparing the dose.





Attaching the Pen Needle

Step 6. Remove the pink paper tab from the back of a new pen needle. Use a new needle for each injection. **Never reuse needles.**

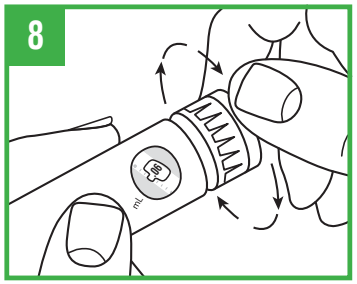
Step 7. Holding the **APOKYN Pen** by the teal cartridge holder, push the pen needle unit onto the pen. Screw the threaded hub of the pen needle onto the teal cartridge holder counter-clockwise. When the needle unit is attached, remove the outer shield that protects the needle with a gentle pull. Save the outer shield. You will use it to remove the needle from the pen after the injection is finished. **Do not** remove the inner needle shield at this time. **The needle is sterile and must stay clean. After opening, do not place the needle on a surface or let it touch anything.**

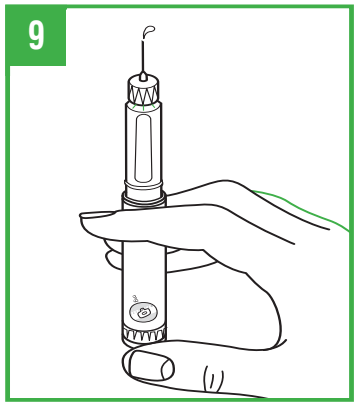
Preparing (Priming) the APOKYN Pen for Use

IMPORTANT – Prior to each injection, it is important that the **APOKYN Pen** be properly primed.

For a new APOKYN Cartridge (1 that has **not** been used before), repeat the priming procedure described on the next page (Steps 8-9) 3 or 4 times to make sure all the air has been removed from the needle and cartridge.

For an APOKYN Cartridge you have used before (1 that has been previously primed), repeat the priming procedure described on the next page (Steps 8-9) **1 time** to make sure all the air has been removed from the needle and cartridge.



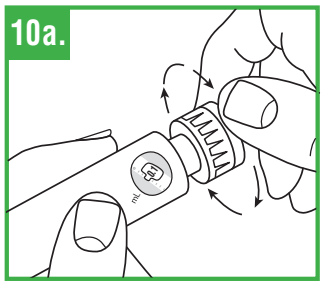


Step 8. You must prepare (prime) the **APOKYN Pen** for use before injecting the medicine. To prime the **APOKYN Pen,** set the dose by turning the dose knob to 0.1 mL. This is important so you can get rid of any air bubbles in the cartridge.

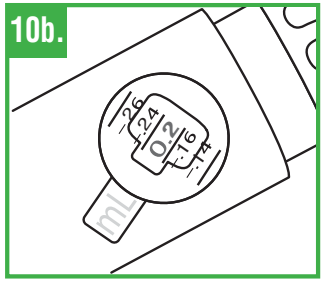
Step 9. Remove the inner needle shield. Remember, **do not** let the needle touch anything. With the needle pointing up, firmly push the injection button in as far as it will go and hold for at least 5 seconds. A small stream of medicine must come out of the end of the needle. If it does not, reset the dose by repeating Step 8. Repeat these steps (Steps 8-9) until a small stream of medicine comes out the end of the needle. When medicine comes out of the end of the needle, the **APOKYN Pen** is primed for injection and ready to use.

APOKYN medicine can cause staining to fabric and other surfaces it touches. Be careful where you prime the **APOKYN Pen.**

10a.

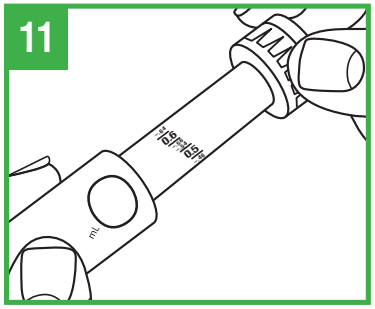


10b.

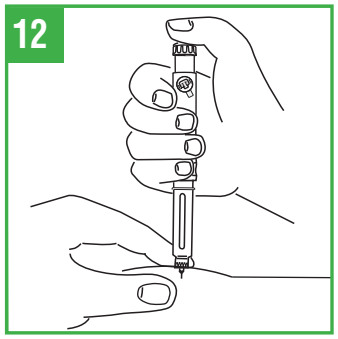


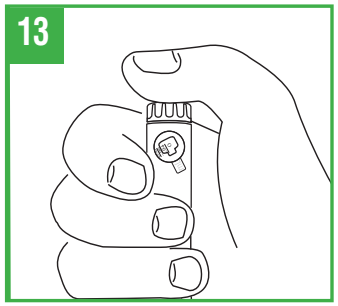
Setting the Dose

Step 10. To set the dose, turn the white dose knob until the correct dose (number of mLs) is shown in the window. The dose will appear as a red number between two black lines that will line up next to the letters “mL” on the pen body. Make sure the correct number (dose) appears in the window.



Step 11. **Dose Correction.** If you turn the dose knob past your dose, **do not** dial backwards. If you dial backwards, APOKYN will be pushed through the needle and you will lose medicine. Continue to turn the dial until it is fully turned. Press the injection button fully. This will reset the dial to zero without pushing medicine out of the needle. Repeat Step 10 to redial your dose.





Giving the Injection

Step 12. **APOKYN** is only for injection under the skin (subcutaneous injection). Choose an injection site on your stomach area, upper arm or upper leg. Change the site with each injection. **Do not** inject **APOKYN** into skin that is red or sore.

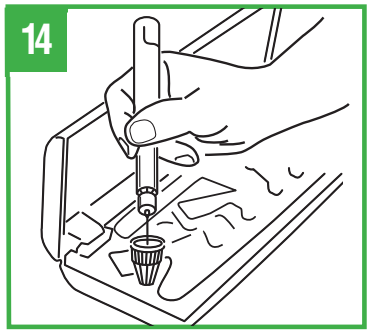
Clean the site with an alcohol swab and allow to air dry. Pinch about an inch of skin and fat tissue of your injection site between your thumb and forefinger. With the other hand, insert the needle all the way into the pinched skin.

Step 13. Fully push the teal injection button on the **APOKYN Pen.** A clicking sound will be heard while the dose is injected. Push the injection button firmly for 5 seconds. Remove the needle from your skin. If medicine keeps dripping from the needle, keep the needle in the skin longer the next time you inject **APOKYN.**

IMPORTANT – If you set your dose and cannot depress the teal injection button, the cartridge is empty. Remove the pen needle and cartridge and prepare the pen as described in Steps 2-9 with a new cartridge. Set the dose and give the injection.

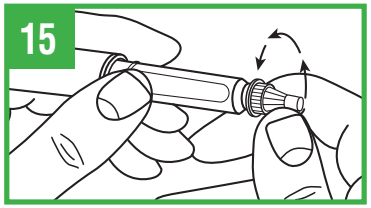
If you set your dose and the injection button stops before you receive a complete dose, note the number in the window, remove the pen needle and cartridge, and prepare the pen as described in Steps 2-9 with a new cartridge. Set the dose to the number that last appeared in the window and administer the injection. This completes the dose.

Before attempting to replace a cartridge, be sure that a needle unit is not attached to the **APOKYN Pen.**



Removing the Pen Needle

Step 14. Carefully replace the outer needle shield. Be careful to avoid a needle-stick. Place the outer needle shield in the notch located on the far left side of your carrying case. The opening of the needle shield should be pointing up. Carefully insert the needle (attached to the pen) into the opening of the shield. **Without holding onto the shield,** push down firmly.



Step 15. Hold the pen by the teal cartridge holder and unscrew the pen needle from the cartridge holder. Recap the pen. **Never recap the pen with a needle attached.** Safely dispose of used pen needles in a "sharps" container. Your specialty pharmacy provider will provide you with a "sharps" container. **Do not throw used needles in a trash can.**

Storage Information

–Store APOKYN cartridges at room temperature, 68°F to 77°F (20°C to 25°C)

Excursions permitted to 59 to 86°F (15 to 30°C) [See USP Controlled Room Temperature]

Proper Disposal

- Put your used needles and syringes in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  – made of a heavy-duty plastic
  – able to be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  – upright and stable during use
  – leak-resistant
  – properly labeled to warn of hazardous waste inside the container

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Care and Storage

The **APOKYN Pen** can now be stored in its carrying case. **Never store or carry the APOKYN Pen with a pen needle attached.**

You must store and care for your pen the right way:

- Avoid exposure to dust, moisture, and cold or hot temperatures.
- Never wash the pen in water or use strong disinfectants. Only a clean, damp cloth should be used for cleaning.
- **Do not** try to repair the pen if it is damaged or if you cannot solve a problem shown in the following “Troubleshooting” section.
- **Do not** use pen for more than 1 year after the first use or after the expiration date on the carton.

For more information, call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).

Troubleshooting

PROBLEM	POSSIBLE CAUSE	HOW TO FIX THE PROBLEM
No medicine comes out of the pen (the dosage dial moves freely, but no click is heard).	The pen is in dose correction mode.	Push the injection button all the way in so the dial returns to zero.
The dosage dial does not return to zero during an injection.	The cartridge is empty.	Replace the cartridge as described in Steps 3-5.
	The pen needle is clogged.	Replace the pen needle as described in Steps 14 & 6-7.
The dosage dial does not turn easily.	Dust or dirt is on the pen.	Turn the dial past the highest setting on the pen. Wipe all exposed pen surfaces with a clean, damp cloth.
Pen does not close.	Cartridge is inserted incorrectly.	Remove cartridge and reload it. See Steps 3-4.

Troubleshooting

PROBLEM	POSSIBLE CAUSE	HOW TO FIX THE PROBLEM
Injection button will not depress.	Cartridge is empty.	Replace cartridge. See Steps 3-5.
Injection button stops before a complete dose is delivered.	Not enough medication in cartridge to complete the dose.	Replace cartridge. See Steps 3-5.
Pen does not work.	Mechanical failure.	Replace pen. Call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).
Dose numbers and/or white markers wear off.	Repeated use over extended period of time.	Replace pen. Call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).

Troubleshooting

PROBLEM	POSSIBLE CAUSE	HOW TO FIX THE PROBLEM
Too much force needed to depress injection button.	Defective cartridge.	Replace cartridge. See Steps 3-5.
Unable to read the dose numbers through the dose window.	Incorrect cleaning or improper handling.	Replace pen. Call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).

For more information, call your specialty pharmacy provider or 1-877-7APOKYN (727-6596).

Patient Information

APOKYN® (AY-po-kin) **(apomorphine hydrochloride injection)**

Read this Patient Information before you start using APOKYN and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is APOKYN?

APOKYN is a prescription medicine used to treat acute, intermittent episodes of poor mobility called *"off"* episodes (end-of-dose wearing *"off"* or unpredictable *"on-off"* episodes) in people with advanced Parkinson's disease (PD).

It is not known if APOKYN is safe and effective in children.

Who should not take APOKYN?

Do not take APOKYN if you are:

- taking certain medicines to treat nausea called $5HT_3$ antagonists including, ondansetron, granisetron, dolasetron, palonosetron, and alosetron. People taking ondansetron together with apomorphine, the active ingredient in APOKYN, have had very low blood pressure and lost consciousness or "blacked out."
- allergic to apomorphine hydrochloride or to any of the ingredients in APOKYN and experience hives, itching, rash, or swelling (e.g., eyes, tongue, etc.). APOKYN also contains a sulfite called sodium metabisulfite. Sulfites can cause severe, life-threatening allergic reactions in some people. An allergy to sulfites is not the same as an allergy to sulfa. People with asthma are more likely to be allergic to sulfites. Call your healthcare provider if you have hives, itching, rash, swelling of the eyes, tongue, lips, chest pain, trouble breathing or swallowing. See the end of this leaflet for a complete list of ingredients in APOKYN.

What should I tell my healthcare provider before taking APOKYN?

Before you start using APOKYN, tell your healthcare provider if you:

- have difficulty staying awake during the daytime
- have dizziness
- have fainting spells
- have low blood pressure
- have asthma
- are allergic to any medicines containing sulfites
- have liver problems
- have kidney problems
- have heart problems
- have had a stroke or other brain problems
- have a mental problem called a major psychotic disorder

- drink alcohol
- are pregnant or plan to become pregnant. It is not known if APOKYN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if APOKYN passes into your breast milk. You and your healthcare provider should decide if you will take APOKYN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using APOKYN with certain other medicines may affect each other. Using APOKYN with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I use APOKYN?

- Read the Instructions for Use starting on page 6 of this leaflet for specific information about the right way to use APOKYN.
- Use APOKYN exactly as your healthcare provider tells you to use it.
- Your healthcare provider will tell you how much APOKYN to use and teach you the right way to use it.
- Your healthcare provider may change your dose if needed.
- **Do not** change your dose of APOKYN or use it more often than prescribed unless your healthcare provider has told you to.
- **Do not** give another dose of APOKYN sooner than 2 hours after the last dose.
- Your healthcare provider will prescribe APOKYN that comes in prefilled glass cartridges that are used with a special multiple-dose injector pen.
- Your APOKYN pen is dosed in milliliters (mL), **not** milligrams (mg). Make sure your prescription tells you how many milliliters (mL) to use.
- Inject APOKYN under your skin (subcutaneously). **Do not** inject APOKYN into a vein.

- Keep a record of how much APOKYN you have used each time you inject or your care partner gives you an injection.
- Use a new needle with each injection. Never reuse a needle.
- APOKYN is a clear and colorless liquid. Do not use APOKYN if it appears cloudy, colored, or to contain particles, and call your pharmacist.
- Your healthcare provider may prescribe another medicine called an antiemetic to take while you are using APOKYN. Antiemetic medicines help to decrease the symptoms of nausea and vomiting that can happen with APOKYN.
- If you take too much APOKYN, call your healthcare provider. If you experience severe or serious side effects such as chest pain or prolonged erection lasting more than 4 hours, go to the nearest hospital emergency room.

What should I avoid while using APOKYN?

- **Do not** drink alcohol while you are using APOKYN. It can increase your chance of developing serious side effects.
- **Do not** take medicines that make you sleepy while you are using APOKYN.

- **Do not** drive, operate machinery, or do other dangerous activities until you know how APOKYN affects you.
- **Do not** change your body position too fast. Get up slowly from sitting or lying. APOKYN can lower your blood pressure and cause dizziness or fainting.

What are the possible side effects of APOKYN?

APOKYN may cause serious side effects. Call your healthcare provider right away if you have any of the serious side effects, including:

- **allergic reaction.** An allergic reaction with side effects of hives, itching, rash, swelling (e.g., eyes, tongue, etc.); trouble breathing and/or swallowing may occur after injecting APOKYN.
- **blood clots.** Injecting APOKYN into a vein (intravenous) can cause blood clots. **Do not** inject APOKYN in your vein.
- **nausea and vomiting.** Severe nausea and vomiting can happen with APOKYN. Your healthcare provider may prescribe a medicine called trimethobenzamide (Tigan®) to help prevent nausea and vomiting. Some patients can stop taking Tigan after using APOKYN for several months. Some patients may need to keep taking Tigan to help prevent nausea and vomiting. Talk to your healthcare provider before you stop taking Tigan.

- **sleepiness or falling asleep during the day.** Some people treated with APOKYN may get sleepy during the day or fall asleep without warning while doing everyday activities such as talking, eating, or driving a car.
- **dizziness.** APOKYN can lower your blood pressure and cause dizziness. Dizziness can happen when APOKYN treatment is started or when the APOKYN dose is increased. **Do not** get up too fast from sitting or after lying down, especially if you have been sitting or lying down for a long period of time.
- **falls.** The changes that can happen with Parkinson's disease (PD), and the effects of some PD medicines, can increase the risk of falling. APOKYN may also increase your risk of falling.
- **hallucinations or psychotic-like behavior.** APOKYN can cause or worsen psychotic-like behavior including hallucinations (seeing or hearing things that are not real), confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs (believing things that are not real), and disorganized thinking.
- **sudden uncontrolled movements** (dyskinesias). Some people with PD may get sudden, uncontrolled movements after treatment with some PD medicines. APOKYN can cause or make dyskinesias worse.
- **intense urges.** Some people with PD have reported new or increased gambling urges, increased sexual urges, and other intense urges, while taking PD medicines, including APOKYN.

- **heart problems.** If you have shortness of breath, fast heartbeat, or chest pain while taking APOKYN, call your healthcare provider or get emergency help right away.
- **serious heart rhythm changes (QT prolongation).** Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint.
- **injection site problems.** Bruising, swelling, and itching can happen at the site where you inject APOKYN.
- **fever and confusion.** This can happen in some people when their PD medicine is stopped or there is a fast decrease in the dose of their PD medicine.
- **skin cancer (melanoma).** Some people with PD may have an increased chance of getting a skin cancer called melanoma. People with PD should have a healthcare provider check their skin for skin cancer regularly.
- **tissue changes (fibrotic complications).** Some people have had changes in the tissues of their pelvis, lungs, and heart valves when taking medicines called nonergot derived dopamine agonists like APOKYN.
- **prolonged painful erections (priaprism).** APOKYN may cause prolonged, painful erections in some people. If you have an erection that lasts more than 4 hours you should call your healthcare provider or go to the nearest hospital emergency room right away.

- **swelling of ankles/legs.** APOKYN may cause swelling, especially in the ankles or legs. Tell your healthcare provider if you notice any swelling.

Other common side effects of APOKYN include:

- yawning
- runny nose
- confusion
- swelling of your hands, arms, legs, and feet

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of APOKYN. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store APOKYN?

- Store APOKYN at room temperature, 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.

Keep APOKYN and all medicines out of the reach of children.

General information about the safe and effective use of APOKYN.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use APOKYN for a condition for which it was not prescribed. Do not give APOKYN to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about APOKYN. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about APOKYN that is written for health professionals.

For more information, go to www.apokyn.com or call 1-877-727-6596.

What are the ingredients in APOKYN?

Active ingredient: apomorphine hydrochloride, USP

Inactive ingredients: sodium metabisulfite, NF, benzyl alcohol, NF, water for injection, USP. It may also contain sodium hydroxide, NF and/or hydrochloric acid, NF.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by: US WorldMeds, LLC
Louisville, KY 40207
Revised: July 2014

US WorldMeds, LLC is the exclusive licensee and distributor of APOKYN in the United States and Its territories.

INS10001.01

BD Medical–Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417, USA

19.3. APPENDIX III: APO-go® Summary of Product Characteristics

APO-go Pen 10mg/ml Solution for Injection

Summary of Product Characteristics Updated 04-Jan-2017 | Britannia Pharmaceuticals Limited

1. Name of the medicinal product

APO-go PEN 10 mg/ml Solution for Injection*

Abbreviated to* APO-go Pen *in the text

2. Qualitative and quantitative composition

1ml contains 10mg apomorphine hydrochloride

Each 3ml PEN contains 30mg apomorphine hydrochloride

Excipient: Sodium bisulphite 0.93mg per ml

For a full list of excipients, see Section 6.1

3. Pharmaceutical form

Solution for injection.

The solution is clear, practically colourless, odourless and free from visible particles.

pH = 3.0 to 4.0

4. Clinical particulars

4.1 Therapeutic indications

The treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication.

4.2 Posology and method of administration

Selection of patients suitable for APO-*go injections:*

Patients selected for treatment with APO-go should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk (see section 4.4).

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting APO-go treatment.

Adults

Administration

APO-go Pen 10mg/ml Solution for Injection is for subcutaneous use by intermittent bolus injection.

Apomorphine must not be used via the intravenous route.

Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used.

Determination of the threshold dose.

The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:

1mg of apomorphine HCl (0.1ml), that is approximately 15-20 micrograms/kg, may be injected subcutaneously during a hypokinetic, or 'off' period and the patient is observed over 30 minutes for a motor response.

If no response, or an inadequate response, is obtained a second dose of 2 mg of apomorphine HCl (0.2ml) is injected subcutaneously and the patient observed for an adequate response for a further 30 minutes.

The dosage may be increased by incremental injections with at least a forty minute interval between succeeding injections, until a satisfactory motor response is obtained.

Establishment of treatment.

Once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response.

The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, remains relatively constant for each patient.

Precautions on continuing treatment.

The daily dose of APO-go varies widely between patients, typically within the range of 3-30mg, given as 1-10 injections and sometimes as many as 12 separate injections per day.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100mg and that individual bolus injections should not exceed 10mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Children and adolescents:

APO-go Pen 10mg/ml Solution for Injection is contra-indicated for children and adolescents under 18 years of age (see section 4.3).

Elderly:

The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of APO-go. The management of elderly patients treated with APO-go has not differed from that of younger patients. However, extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension.

Renal impairment:

A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment (see section 4.4).

4.3 Contraindications

In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

Apomorphine HCl treatment must not be administered to patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia.

APO-go should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product.

APO-go is contraindicated for children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

Apomorphine HCl should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients.

Since apomorphine may produce hypotension, even when given with domperidone pre-treatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as anti-hypertensives, and especially in patients with pre-existing postural hypotension.

Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying

heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG should be performed:

- prior to treatment with domperidone

- during the treatment initiation phase

- as clinically indicated thereafter

The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy.

At each medical visit, risk factors should be revisited.

Apomorphine is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid to areas of nodularity and induration.

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine.

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range (see section 4.5).

Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients.

Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage may be considered.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

APO-go Pen 10mg/ml Solution for Injection contains sodium bisulphite which may rarely cause severe allergic reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per 10ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Patients selected for treatment with apomorphine HCl are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of apomorphine HCl therapy the patient should be monitored for unusual side-effects or signs of potentiation of effect.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications.

The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

Antihypertensive and Cardiac Active Medicinal Drugs

Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products (See section 4.4).

It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

4.6 Fertility, pregnancy and lactation

There is no experience of apomorphine usage in pregnant women.

Animal reproduction studies do not indicate any teratogenic effects, but doses given to rats which are toxic to the mother can lead to failure to breathe in the newborn. The potential risk for humans is unknown. See Section 5.3.

APO-go should not be used during pregnancy unless clearly necessary.

It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with APO-go should be made taking into account the benefit of breast-feeding to the child and the benefit of APO-go to the woman.

4.7 Effects on ability to drive and use machines

Apomorphine HCl has minor or moderate influence on the ability to drive and use machines.

Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see Section 4.4).

“This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

  o The medicine has been prescribed to treat a medical or dental problem and

  o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

  o It was not affecting your ability to drive safely”

4.8 Undesirable effects

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Uncommon:

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine.

Rare:

Eosinophilia has rarely occurred during treatment with apomorphine HCl.

Immune system disorders

Rare:

Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur.

Psychiatric disorders

Very Common:

Hallucinations

Common:

Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine HCl therapy.

Not known:

Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine (see section 4.4).

Aggression, agitation

Nervous system disorders

Common:

Transient sedation with each dose of apomorphine HCl at the start of therapy may occur; this usually resolves over the first few weeks.

Apomorphine is associated with somnolence.

Dizziness / light-headedness have also been reported.

Uncommon:

Apomorphine may induce dyskinesias during 'on' periods, which can be severe in some cases, and in a few patients may result in cessation of therapy.

Apomorphine has been associated with sudden sleep onset episodes (see section 4.4).

Not known:

Syncope

Vascular disorders

Uncommon:

Postural hypotension is seen infrequently and is usually transient (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Common:

Yawning has been reported during apomorphine therapy.

Uncommon:

Breathing difficulties have been reported.

Gastrointestinal disorders

Common:

Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone (see section 4.2).

Skin and subcutaneous tissue disorders

Uncommon:

Local and generalised rashes have been reported.

General disorders and administration site conditions

Very common:

Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur.

Uncommon:

Injection site necrosis and ulceration have been reported.

Not known:

Peripheral oedema has been reported.

Investigations

Uncommon:

Positive Coombs' tests have been reported for patients receiving apomorphine.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Ireland

HPRA Pharmacovigilance,

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

Malta

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as suggested below:-

Excessive emesis may be treated with domperidone.

Respiratory depression may be treated with naloxone.

Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed.

Bradycardia may be treated with atropine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmatherapeutic group: Dopamine agonists

ATC Classification: N04B C07

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa.

Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans.

5.2 Pharmacokinetic properties

After subcutaneous injection of apomorphine its fate can be described by a two-compartment model, with a distribution half-life of 5 (± 1.1) minutes and an elimination half-life of 33 (± 3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the drug distribution being best described by a two-compartment model. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and that the brief duration of clinical action of the drug (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described.

5.3 Preclinical safety data

Repeat- dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the SmPC.

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in the *in vivo* studies performed.

The effect of apomorphine on reproduction has been investigated in rats. Apomorphine was not teratogenic in this species, but it was noted that doses which are toxic to the mother can cause loss of maternal care and failure to breathe in the newborn.

No carcinogenicity studies have been performed.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium bisulphite (E222)

Hydrochloric Acid (37%), concentrated (to adjust pH to 3.0 –4.0)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

48 hours after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the container in the outer carton to protect from light.

The product should be stored at the same conditions after opening and between withdrawals.

6.5 Nature and contents of container

Cartridge.

APO-go Pen 10 mg/ml is a disposable multiple dose pen injector system incorporating a clear glass (type I) cartridge containing a clear solution for injection. The glass cartridge is sealed at one end with a bromobutyl rubber piston, and at the other end with a bromobutyl rubber/aluminium membrane.

Each pen contains 3ml of solution for injection.

Packs containing 1, 5, or 10 x 3ml pens in a moulded plastic tray in an outer cardboard carton.

Not all pack sizes may be marketed.

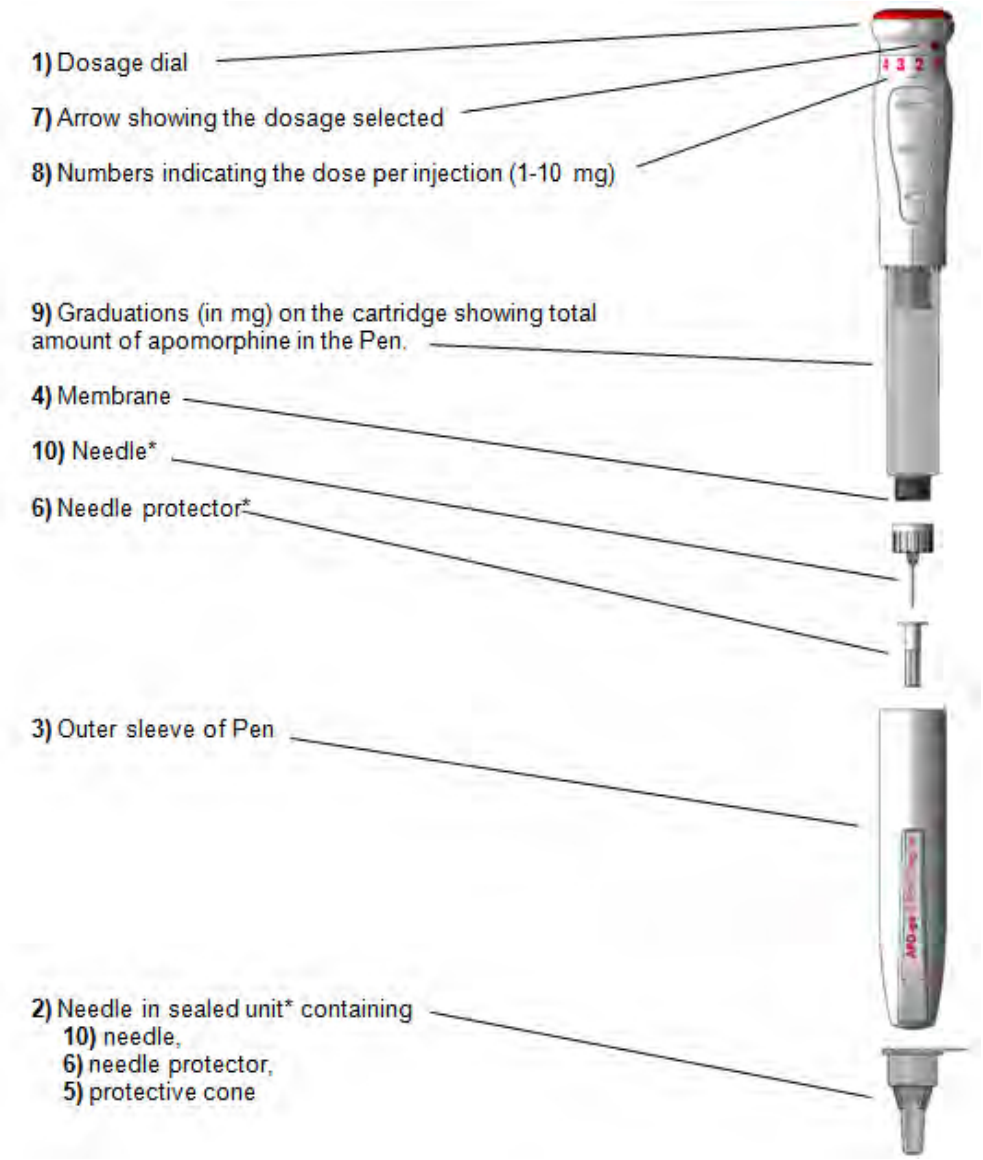
6.6 Special precautions for disposal and other handling

APO-go PEN

Do not use if solution has turned green.

Discard each pen no later than 48 hours from first use.

(see attached diagram)



* This pack does NOT contain needles for use with your Pen.

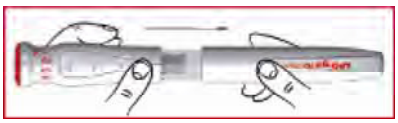
Use pen needles not more than 12mm (½") in length and not finer than 0.33mm (29 G). Pen needles recommended for use with insulin pens are compatible with APO-go® Pen.

IMPORTANT: Do not pull the red capped dial (see 1) before you have set the dosage (see 'Selecting the correct dosage').

Attaching the needle

(a) Before using APO-go Pen you will need some surgical wipes and one needle in its protective cone (**see 2**).

(b) Take the Pen out of its box and remove the outer sleeve (**see 3**).



(c) Wipe the membrane of the Pen (**see 4**) with a surgical wipe.

(d) Peel off the paper from the needle cone (**see 2**).

(e) It is important to bring the needle to the Pen in a straight line, as shown above. If the needle is presented at an angle it may cause the Pen to leak.

(f) Screw the cone (**see 2**) clockwise onto the membrane until it is tight. This securely attaches the needle.

(g) Remove the protective cone (**see 5**), but do not throw it away. Do not remove the needle protector (**see 6**) at this stage.

(h) Replace the Pen's outer sleeve (**see 3**).

Selecting the correct dose

(i) Press the red capped dosage dial (**see 1**) and whilst holding it down, turn the dial clockwise until the arrow points to the dose your doctor chose for you (**see 7**&**8**). Release the downward pressure on the red capped dial. The dose is now set and you do not need to redial for subsequent injections.

Important: If you pass your prescribed dose while turning the dial, just continue pressing and turning in the same direction until the arrow points to the dose your doctor chose for you.

Never pull and turn the red capped dosage dial at the same time.

If your dose is 1 mg, start by emptying a 1 mg dose onto a paper tissue and discarding it. This is called 'priming' and is important because it ensures you get a full dose the first time you use your Pen. Then, set the dose you require for

injection and inject it in the usual way (see “Injecting”). If the first dose required is more than 1 mg, you do not need to prime the Pen.

Injecting

(j) Once you have set the dose, gently pull out the red capped dosage dial as far as it will go. Check the red scale on the plunger (**see 9**) and inject only if the line that is just visible matches the intended dose.


(k) Using a surgical wipe, clean the area of skin where you plan to inject the medicine and around it.

(l) Remove the Pen's outer sleeve (**see 3**).

(m) Remove the needle protector (**see 6**).

(n) Insert the needle (**see 10**) into the skin as shown by your doctor.

(o) To inject, press the red capped dosage dial (**see 1**) down as far as it will go, using your thumb if possible. Once the red capped dosage dial is fully depressed, count to three before withdrawing the needle.

(p) Replace the protective cone (**see 5**) onto the used needle and push gently into place. Once secure, turn the needle anti-clockwise to unscrew it.

Keep the needle in its protective cone and discard it in a safe place, such as a “Sharps” bin or an empty coffee jar.


Preparing for the next injection

(q) Remove the outer sleeve of the Pen and check there is enough apomorphine left in the cartridge for your next injection. If there is, put a new needle in place in the same way as before.

(r) If there is not enough apomorphine left for another injection, prepare another pen.

(s) Finally, replace the outer sleeve of your Pen.

7. Marketing authorisation holder

Britannia Pharmaceuticals Limited

200 Longwater Avenue,

Green Park,

Reading,

Berkshire

RG2 6GP

United Kingdom

8. Marketing authorisation number(s)

PL 04483/0073

PA 356/10/1

MA 957/00102

9. Date of first authorisation/renewal of the authorisation

31 March 1999 / 27 July 2009

10. Date of revision of the text

10/2016

Company Contact Details

Britannia Pharmaceuticals Limited
http://www.britannia-pharm.co.uk/

Address

200 Longwater Avenue, Green Park, Reading, Berkshire, RG2 6GP, UK

Medical Information Direct Line

+44 (0)870 851 0207

Telephone

+44 1189209500

Medical Information e-mail

enquiries@medinformation.co.uk

19.4. APPENDIX IV: Regulations and Guidelines

19.4.1. Declaration of Helsinki

The Policy of the World Medical Association is available at URL: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

19.4.2. Approval by an IRB/REB/IEC

This protocol must be reviewed and approved by a valid IRB/REB/IEC prior to initiation of the study. Written notification of approval is to be submitted by the Investigator to Sunovion monitor prior to shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval will consist of a completed Institutional Review Board Approval form or Research Ethics Board Approval form, or written documentation from the IRB or REB containing the same information.

Until written approval by the IRB/REB/IEC has been received by the Investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB/REB/IEC. Written approval from the IRB/REB/IEC, or a designee, must be received by Sunovion, before implementation. This written approval will consist of a completed approval form, or written documentation from the IRB/REB/IEC containing the same information.

19.4.3. Regulatory Authority/Agency

For Investigational New Drug (IND) studies, the minimum standards of study conduct and requirements for informed consent are defined in the applicable regulations of the country in which the study is conducted.

This protocol must be reviewed and approved by the country specific Regulatory Authority/Agency prior to initiation of the study. The Sponsor or authorized delegate will be responsible for the submission.

19.5. APPENDIX V: Modified Hoehn and Yahr Scale

Modified Hoehn & Yahr

0:	Asymptomatic.
1:	Unilateral involvement only.
1.5:	Unilateral and axial involvement
2:	Bilateral involvement without impairment of balance.
2.5:	Mild bilateral disease with recovery on pull test.
3:	Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
4:	Severe disability; still able to walk or stand unassisted.
5:	Wheelchair bound or bedridden unless aided.

19.6. APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Past X Years or Lifetime

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

- ***What did you do?***
- ***Did you_____ as a way to end your life?***
- ***Did you want to die (even a little) when you_____?***
- ***Were you trying to end your life when you _____?***
- ***Or did you think it was possible you could have died from_____?***

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? *(*Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ No ☐

Total # of Attempts _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior? Yes ☐ No ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ No ☐

Total # of interrupted _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ No ☐

Total # of aborted _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ No ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Since Last Visit

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____ as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts: _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ **No** ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted: _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted: _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

Suicide:

Yes ☐ **No** ☐

Answer for Actual Attempts Only

Most Lethal Attempt Date:

Actual Lethality/Medical Damage:

Enter Code: _____

0. No physical damage or very minor physical damage (e.g., surface scratches).
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Potential Lethality: Only Answer if Actual Lethality=0

Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

Enter Code: _____

0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

19.7. APPENDIX VII: United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria

Step 1 - Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 - Exclusion criteria for PD

- History of repeated strokes with stepwise progression of Parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communication hydrocephalus on imaging study
- Negative response to large doses of L-Dopa in absence of malabsorption
- MPTP exposure

Step 3 - Supportive prospective positive criteria for PD

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most

- Excellent response (70-100%) to L-Dopa
- Severe L-Dopa-induced chorea
- L-Dopa response for 5 years or more
- Clinical course of ten years or more

Reference: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55(3):181-4.