

## 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**  
**Initial U.S. Approval: 2004**

### RECENT MAJOR CHANGES

Warnings and Precautions, Hemolytic Anemia (5.8) 5/2022

### 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 (6 mg) (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 (2.5)
- 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

Injection; 30 mg/3 mL (10 mg/mL) as a clear, colorless, sterile solution available in single-patient-use cartridges (3, 16)

### CONTRAINDICATIONS

- Concomitant use of APOKYN with 5HT<sub>3</sub> antagonists, including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated (4)

- Hypersensitivity to apomorphine, its excipients or sodium metabisulfite (4, 5.13)

### 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)
- Falls may occur, or increase (5.5)
- May cause hallucinations and psychotic-like behavior (5.6)
- May cause dyskinesia or exacerbate pre-existing dyskinesia (5.7)
- May cause hemolytic anemia (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 MDD US Operations, LLC at 1-877-727-6596 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (7.4)

### 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: 5/2022

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## 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<sub>3</sub> 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 (20mg). -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 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 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 for single-patient-use is used with a manual reusable 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 pen injector is provided in a package with six needles.

#### 4 CONTRAINDICATIONS

APOKYN is contraindicated in patients:

- Using concomitant drugs of the 5HT<sub>3</sub> 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 to apomorphine or to any of the excipients of APOKYN, including a sulfite (i.e., sodium metabisulfite). Angioedema or anaphylaxis may occur [*see Warnings and Precautions (5.13)*].

#### 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 / Hypotension / Orthostatic Hypotension**

In clinical studies, approximately 2% of APOKYN-treated patients experienced syncope. 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 ( $\geq 20$  mm Hg decrease) when evaluated at various times after in-office dosing. A small number of patients developed severe systolic orthostatic hypotension ( $\geq 30$  mm Hg decrease and systolic BP  $\leq 90$  mm Hg) 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)*].

In a study of healthy subjects, the hypotensive effect of APOKYN on systolic and diastolic blood pressure was exacerbated by the concomitant use of alcohol or sublingual nitroglycerin (0.4 mg). Patients should avoid alcohol when using APOKYN [see *Drug Interactions (7.3)*]. Patients taking APOKYN should lie down before and after taking sublingual nitroglycerin. Other vasodilators and antihypertensives may also increase the hypotensive effects of APOKYN. Monitor blood pressure for hypotension and orthostatic hypotension in patients taking APOKYN with concomitant antihypertensive medications or vasodilators [see *Drug Interactions (7.2, 7.3)*].

## 5.5 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.

## 5.6 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)*].

## 5.7 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.

## 5.8 Hemolytic Anemia

Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment in the postmarketing setting. Many of the reported cases included positive direct antiglobulin test (Coombs test), suggesting a potential immune-mediated hemolysis. Severe anemia, angina, and dyspnea have occurred with hemolytic anemia. Some patients were treated with high dose glucocorticoids or blood transfusions. Hemolytic anemia can appear at any time after apomorphine treatment. If a patient develops anemia while taking APOKYN, consider a workup for hemolytic anemia. If hemolytic anemia occurs, consider discontinuing APOKYN treatment.

## 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 dose related prolongation of QTc interval after apomorphine exposure similar to that achieved with therapeutic doses of APOKYN [*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 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 Hypersensitivity**

Hypersensitivity/allergic reactions characterized by urticaria, rash, pruritus, and/or various manifestations of angioedema may occur because of APOKYN or because of its sulfite excipient. APOKYN contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

### **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 [ $\text{mg}/\text{m}^2$ ] 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  $\text{mg}/\text{m}^2$  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 serious adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling:

- Serious Adverse Reactions After Intravenous Administration [*see Warnings and Precautions (5.1)*]
- Nausea and Vomiting [*see Warnings and Precautions (5.2)*]
- Falling Asleep During Activities of Daily Living and Somnolence [*see Warnings and Precautions (5.3)*]
- Syncope/Hypotension/Orthostatic Hypotension [*see Warnings and Precautions (5.4)*]
- Falls [*see Warnings and Precautions (5.5)*]
- Hallucinations/Psychotic-Like Behavior [*see Warnings and Precautions (5.6)*]
- Dyskinesias [*see Warnings and Precautions (5.7)*]
- Hemolytic Anemia [*see Warnings and Precautions (5.8)*]
- Impulse Control/Compulsive Behaviors [*see Warnings and Precautions (5.9)*]
- Coronary Events [*see Warnings and Precautions (5.10)*]
- QTc Prolongation and Potential for Proarrhythmic Effects [*see Warnings and Precautions (5.11)*]
- Withdrawal-Emergent Hyperpyrexia and Confusion [*see Warnings and Precautions (5.12)*]
- Hypersensitivity [*see Warnings and Precautions (5.13)*]
- Fibrotic Complications [*see Warnings and Precautions (5.14)*]
- Priapism [*see Warnings and Precautions (5.15)*]

### 6.1 Clinical Trials 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.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of apomorphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Hematologic and Lymphatic Systems:* hemolytic anemia [see *Warnings and Precautions (5.8)*]

## **7 DRUG INTERACTIONS**

### **7.1 5HT<sub>3</sub> Antagonists**

Based on reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron, the concomitant use of APOKYN with 5HT<sub>3</sub> antagonists including antiemetics (for example, ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated.

### **7.2 Antihypertensive Medications and Vasodilators**

In clinical studies, the following adverse events were experienced more commonly in patients receiving concomitant antihypertensive medications or vasodilators (n=94) than in patients not receiving these

medications (n=456): hypotension (10% vs 4%) [see *Warnings and Precautions (5.4)*], myocardial infarction (3% vs 1%), serious pneumonia (5% vs 3%), serious falls (9% vs 3%), and bone and joint injuries (6% vs 2%). Some of the events may be related to the increased incidence of hypotension in patients receiving concomitant antihypertensive medications or vasodilators [see *Warnings and Precautions (5.4, 5.5)*].

Concomitant administration of 0.4 mg sublingual nitroglycerin with APOKYN in healthy subjects causes greater decreases in blood pressure compared to APOKYN alone. When nitroglycerin and APOKYN were concomitantly administered to healthy subjects, the mean largest decrease (the mean of each subject's largest drop in blood pressure measured within the 6-hour period following administration of APOKYN) in supine systolic and diastolic blood pressure (measured over 6 hours) was 9.7 mm Hg and 9.3 mm Hg, respectively [see *Clinical Pharmacology (12.3)*]. The mean largest decrease in standing systolic and diastolic blood pressure was 14.3 mm Hg and 13.5 mm Hg, respectively. Some individuals experienced very large decreases in standing systolic and diastolic blood pressure, up to a maximum decrease of 65 mm Hg and 43 mm Hg, respectively.

In comparison, the mean largest decrease in supine systolic and diastolic blood pressure when APOKYN was administered alone was 6.1 mm Hg and 7.3 mm Hg, respectively, and in standing systolic and diastolic blood pressure was 6.7 mm Hg and 8.4 mm Hg, respectively.

Patients taking APOKYN should lie down before and after taking sublingual nitroglycerin [see *Warnings and Precautions (5.4)*].

### 7.3 Alcohol

Concomitant administration of high dose (0.6 g/kg) or low dose (0.3 g/kg) ethanol with APOKYN in healthy subjects causes greater decreases in blood pressure compared to APOKYN alone.

When high dose ethanol and APOKYN were concomitantly administered to healthy subjects, the mean largest decrease (the mean of each subject's largest drop in blood pressure measured within the 6-hour period following administration of APOKYN) for supine systolic and diastolic blood pressure was 9.1 mm Hg and 10.5 mm Hg, respectively [see *Clinical Pharmacology (12.3)*]. The mean largest standing systolic and diastolic blood pressure decrease was 11.3 mm Hg and 12.6 mm Hg, respectively. In some individuals, the decrease was as high as 61 mm Hg and 51 mm Hg, respectively, for standing systolic and diastolic blood pressure.

When low dose ethanol and APOKYN were concomitantly administered, the mean largest decrease in supine systolic and diastolic blood pressure was 10.2 mm Hg and 9.9 mm Hg, respectively. The mean largest decrease in standing systolic and diastolic blood pressure was 8.4 mm Hg and 7.1 mm Hg, respectively.

In comparison, the mean largest decrease in supine systolic and diastolic blood pressure when APOKYN was administered alone was 6.1 mm Hg and 7.3 mm Hg, respectively, and in standing systolic and diastolic blood pressure was 6.7 mm Hg and 8.4 mm Hg, respectively.

Patients should avoid drinking alcohol after using APOKYN [see *Warnings and Precautions (5.4)*].

### 7.4 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.

## 7.5 **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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 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 administering APOKYN to patients with mild and moderate hepatic impairment because of the increased  $C_{max}$  and AUC in these patients. Closely monitor patients with mild and moderate hepatic impairment. Studies of subjects with severe hepatic impairment have not been conducted [see *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.

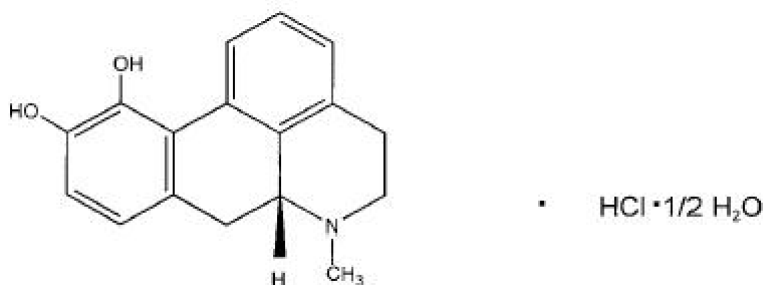
## 10 OVERDOSAGE

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 6 $\alpha$ -Aporphine-10,11-diol hydrochloride hemihydrate with a molecular formula of  $C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2} H_2O$ . 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 (equivalent to 8.55 mg apomorphine), 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<sub>4</sub> receptor, and moderate affinity for the dopamine D<sub>2</sub>, D<sub>3</sub>, and D<sub>5</sub>, and adrenergic  $\alpha_1$ D,  $\alpha_2$ B,  $\alpha_2$ C 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<sub>2</sub>-type receptors within the caudate-putamen in the brain.

### 12.2 Pharmacodynamics

#### Prolongation of the QTc Interval

In a thorough QT study at exposures similar to those achieved with the recommended dosing, apomorphine resulted in a prolongation of QTcF of 10 msec (90% upper confidence interval of 16 msec). The thorough QT study also identified a significant exposure-response relationship between apomorphine concentration and QTcF.

#### Decreases in Blood Pressure

Dose-dependent mean decreases in systolic blood pressure ranged from 5 mm Hg to 16 mm Hg after administration of APOKYN 2 mg and 10 mg, respectively. Dose-dependent mean decreases in diastolic blood pressure ranged from 3 mm Hg to 8 mm Hg after administration of APOKYN 2 mg and 10 mg, respectively. These changes were observed 20 minutes after dosing, and were maximal between 20 and 40 minutes after dosing. Lesser, but still noteworthy blood pressure decreases persisted up to at least 90 minutes after dosing. Effects on blood pressure are additive when APOKYN is coadministered with nitroglycerin or alcohol [*see Drug Interactions (7.3, 7.4)*].

## 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.

### Specific 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  $AUC_{0-\infty}$  and  $C_{max}$  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  $AUC_{0-\infty}$  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 Interaction Studies

#### *Carbidopa/levodopa*

Levodopa pharmacokinetics were unchanged when subcutaneous APOKYN and levodopa were co-

administered 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.

#### *Ethanol and Nitroglycerin*

Co-administration of low dose ethanol (0.3 g/kg) or nitroglycerin (0.4 mg) with APOKYN in healthy subjects did not have a significant impact on the pharmacokinetics of apomorphine, but high dose ethanol (0.6 g/kg), equivalent to approximately 3 standardized alcohol-containing beverages, increased the  $C_{max}$  of apomorphine by about 63%. However, the hypotensive effect of APOKYN was increased by the concomitant use of alcohol or of sublingual nitroglycerin [see *Warnings and Precautions (5.4) and Drug Interactions (7.2, 7.3)*].

#### *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 doses 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.

### Study 1

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

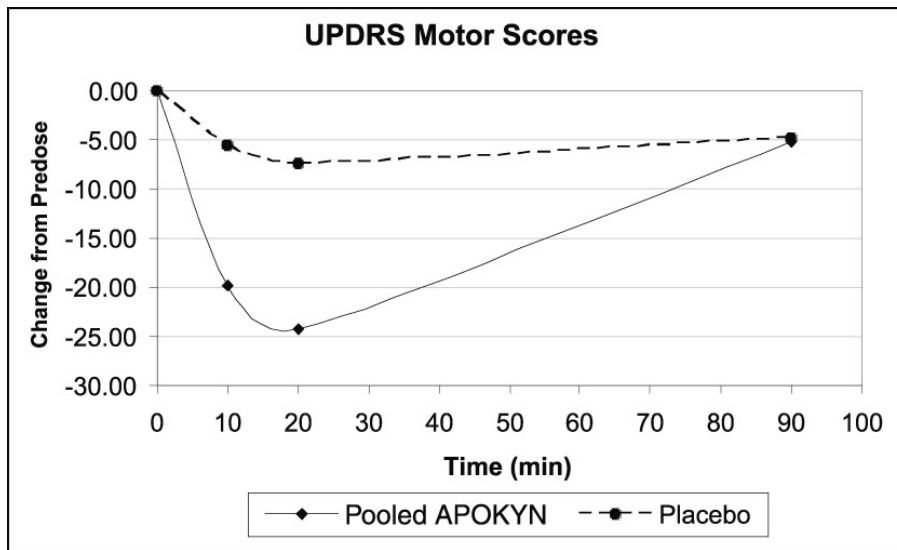
Study 3

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 3**

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 clear, colorless, sterile solution in cartridges, 30 mg/3 mL (10 mg/mL), for single-patient-use with a pen injector (APOKYN Pen).

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

### Administration with the APOKYN Pen

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)*].

### 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

[see *Warnings and Precautions (5.13)*]. Advise patients who experience any hypersensitivity/allergic reaction to APOKYN that they should not take 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)*].

#### 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. Inform patients that alcohol and nitroglycerin (and possibly other vasodilators and antihypertensive medications) may potentiate the hypotensive effect of APOKYN [see *Warnings and Precautions (5.4)*]. Instruct patients ideally to lie down before taking sublingual nitroglycerin and to remain supine and avoid standing for at least 45 minutes after nitroglycerin. Instruct patients taking APOKYN to avoid alcohol while using APOKYN and of the increased hypotensive effects of APOKYN taken with nitroglycerin or by taking APOKYN after alcohol ingestion.

#### Falls

Alert patients that they may have increased risk for falling when using APOKYN [see *Warnings and Precautions (5.5)*].

#### 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 (5.6)*].

#### Dyskinesia

Inform patients that APOKYN may cause and/or exacerbate pre-existing dyskinesias [see *Warnings and Precautions* (5.7)].

#### Hemolytic Anemia

Inform patients and caregivers that hemolytic anemia may occur and to contact their healthcare provider if they develop any signs or symptoms [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)].

#### Priapism

Advise patients that APOKYN may cause prolonged painful erections and that if this occurs 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)].

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