apomorphine (Apokyn®, Kynmobi)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO087

Description

Apomorphine (Apokyn, Kynmobi), a non-ergoline dopamine agonist, is administered as a subcutaneous injection. It possesses an unknown mechanism in the treatment of Parkinson's disease but is suggested that its effects are attributed to stimulation of post-synaptic D(2)-type receptors within the brain.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
apomorphine (Apokyn)	10 mg/mL Subcutaneous Injection	Parkinson's Disease	54 mL/30 days
apomorphine (Kynmobi)	10 mg sublingual film	Parkinson's Disease	150 films/30 days
	15 mg sublingual film		150 films/30 days
	20 mg sublingual film		150 films/30 days
	25 mg sublingual film		150 films/30 days
	30 mg sublingual film		150 films/30 days
	10/15/20/25/30mg titration kit		1 kit/30 days

Initial Evaluation

I. Apomorphine (Apokyn, Kynmobi) may be considered medically necessary when the following criteria below are met:

A. Member is 18 years of age or older; **AND**

B. Must be prescribed by, or in consultation with, a neurologist; **AND**
C. Not used in combination with a 5-HT_3 receptor antagonist (e.g. ondansetron, granisetron, dolasetron, etc.); **AND**
D. A diagnosis of **Parkinson's disease** when the following are met:
    1. Member experiences predictable acute, intermittent hypomobility "off" episodes; **AND**
    2. Provider must attest that the first dose will be done in office and the member will be monitored; **AND**
    3. Member will be taking carbidopa/levodopa concurrently with apomorphine (Apokyn, Kynmobi); **AND**
    4. Treatment with ONE of the following has been ineffective, contraindicated, or not tolerated:
        i. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
        ii. Monoamine oxide-B (MAO-B) inhibitor (e.g. selegiline, rasagiline)
        iii. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone)

II. Apomorphine (Apokyn) is considered investigational when used for all other conditions, including but not limited to:
    A. Erectile dysfunction

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has demonstrated benefit through reduction of "off" episodes/hypomobility

Supporting Evidence

I. Apomorphine subcutaneous injection (Apokyn) was studied in three randomized controlled trials. All patients in the studies were on L-dopa, 86% of patients were on oral dopaminergic agonists, 31% were on catechol-ortho-methyl transferase inhibitors, and 10% were on monoamine B oxidase inhibitors.
    - Study one was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating 29 patients with advanced Parkinson's disease who had at least two hours of "off" time per day. Apomorphine (Apokyn) demonstrated a statistically significant decrease

in the Unified Parkinson's Disease Rating Scale (UPDRS) compared to placebo, with a mean change from baseline of -23.9 and -0.1 (p<0.001) respectively.

- Study two was a randomized, placebo-controlled crossover trial evaluating 17 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS compared to placebo, with a mean change from baseline of -20 and -3 respectively.
- Study three was a randomized, double-blind, placebo-controlled, trial evaluating 62 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS at 20 minutes compared to placebo, with a mean change from baseline of -24.2 vs -7.4 (p<0.0001) respectively.

II. Apomorphine sublingual tablet (Kynmobi) was studied in one phase 3 clinical trial that consisted of an open label dose-titration phase followed by a 12 week randomized, double-blind, placebo-controlled trial in 109 patients who had diagnosis of Parkinson's Disease and had at least two hours of 'off' time per day with predictable morning 'off' periods. Patients continued concomitant Parkinson's Disease medications including levodopa-containing agents (100% apomorphine and placebo group), dopamine agonists (56% apomorphine and placebo group), monoamine oxidase-B inhibitors (41% apomorphine, 44% placebo), amantadine (15% apomorphine, 29% placebo) and catechol-O-methyltransferase inhibitors (9% apomorphine and placebo groups).
    - The primary efficacy endpoint, mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS Part 3 score at week 12, was significantly greater in the apomorphine group compared to placebo (change -11.1, SE 1.46, 95% CI -14.0 to -8.2, with apomorphine sublingual film VS -3.5, 1.29, -6.1 to -0.9, with placebo) with a least squares mean difference of -7.6 (SE 1.96, 95% CI -11.5 to -3.7; p=0.0002).
    - The key secondary endpoint, percentage of patients with a self-rated full on response within 30 minutes at the 12-week visit, was significantly greater in the apomorphine group (35%, SE 21 to 35) compared to placebo (16%, SE 8 to 30) (OR 2.81, 1.04 to 7.64; p=0.043).

III. Use of apomorphine (Apokyn, Kynmobi) with 5-HT_3 antagonists (e.g. ondansetron, granisetron, dolasetron, or alosetron) is contraindicated. There have been reports of profound hypotension and loss of consciousness when administered together.

IV. Adverse events are similar between both the sublingual and subcutaneous formulations of apomorphine (Apokyn, Kynmobi), including syncope, hypotension, orthostatic hypotension, nausea, vomiting, falling asleep during activities of daily living, somnolence, and hallucinations or psychotic-like behavior. Oral mucosal irritation was common during the clinical trials for apomorphine sublingual films (Kynmobi) with approximately 20% of patients developing mild to moderate oral mucosal ulcerations or stomatitis, oral soft tissue pain or paresthesia, oral/pharyngeal soft tissue swelling or oral mucosal erythema.

V. Because of the high incidence of nausea and vomiting with apomorphine (Apokyn, Kynmobi) at recommended doses, a non 5HT-3 antagonist antiemetic (e.g. trimethobenzamide) should be initiated beginning three days prior to starting apomorphine (Apokyn, Kynmobi). Treatment with the antiemetic should be continued only as long as necessary to control nausea and vomiting symptoms, and ideally is discontinued no longer than two months after initiation of apomorphine (Apokyn, Kynmobi).

VI. Due to high incidence of syncope/hypotension/orthostatic hypotension with apomorphine (Apokyn, Kynmobi), dose initiation should occur under the supervision of a healthcare provider where blood pressure and pulse can be monitored according to the package insert.

VII. According to the prescribing information for apomorphine subcutaneous injection (Apokyn), there is no evidence from controlled trials that doses greater than 0.6mL (6mg) gave an increased effect and therefore, individual doses exceeding 0.6mL (6mg) are not recommended. The average frequency of dosing in the developmental program is 3 times per day. Additionally, there is limited experience with single doses greater than 0.6 mL (6mg), dosing more than five times per day, and with total daily doses greater than 2mL (20mg).

VIII. According to the prescribing information for apomorphine sublingual tablets (Kynmobi), the dose range is 10mg to 30mg per dose. The maximum single dose should not exceed 30mg; do not administer more than five doses per day.

Investigational or Not Medically Necessary Uses

I. Apomorphine (Apokyn) has not been adequately studied in patients with erectile dysfunction.

References

1. Apokyn [prescribing information]. USWorldMeds: Louisville, KY; November 2019.
2. Pfeiffer RF, Gutmann L, Hull KL, Bottini PB, Sherry JH. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2007;13(2):93-100.
3. Dewey RB, Hutton JT, Lewitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. Arch Neurol. 2001;58(9):1385-92.
4. Uptodate, Inc. Medical management of motor fluctuations and dyskinesia in Parkinson disease [database online]. Waltham, MA. Updated 09/16/19. Available at: http://www.uptodate.com/home/index.html. [Accessed 11/04/19]
5. Orlanow CW et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomized, double-blind, placebo-controlled phase 3 study. *Lancet Neurol* 2020; 19:135-44.
6. Kynmobi [prescribing information]. Sunovion Pharmaceuticals, Inc.: Marlborough, MA; May 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Added apomorphine sublingual films (Kynmobi) to policy • Added requirement of member is experiencing predictable acute, intermittent hypomobility "off" episodes • Updated renewal criteria to require prior approval through this OR prior health plan (not established via samples) • Removed renal criteria requirement confirming lack of toxicity to therapy • Updated apomorphine subcutaneous injection (Apokyn) QLL to align with FDA label and package size of 3mL/cartridge	03/2021
Criteria transitioned to policy	10/2019
Previous reviews	11/2014 12/2008 09/2008
Criteria created	09/2005