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Policy Number: C6918-A

Apokyn, Kynmobi (apomorphine)

PRODUCTS AFFECTED

Apokyn (apomorphine), Kynmobi (apomorphine film), apomorphine soln cartridge

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Advanced Parkinson's disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. PARKINSONS DISEASE:
   1. Diagnosis of advanced Parkinson's disease (see Appendix)

AND

2. Member is experiencing acute intermittent hypomobility (defined as “off” episodes characterized by muscle stiffness, slow movements, or difficulty starting movements) despite optimized oral PD therapy. Clinical documentation required (includes clinical notes from the member’s medical records including any applicable labs and/or tests, supporting the diagnosis).
   AND
3. Documentation that the member is currently receiving levodopa or levodopa/carbidopa and adjunctive therapy with anti-Parkinson's agents [e.g., dopamine agonists (pramipexole, ropinirole), Catechol-O-methyl transferase (COMT) inhibitor (entacapone, tolcapone), Monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline)], and has been on optimized doses for the last 30 days and continues to experience “off” periods
   AND
4. Prescriber attests member has a concurrent prescription order for trimethobenzamide to pre-medicate for the initial doses of apomorphine as needed
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven’t been addressed by the prescriber within the documentation submitted for review [Contraindications to Apokyn, Kynmobi (apomorphine) include: Concomitant use of apomorphine with 5HT3 antagonists, including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron, hypersensitivity to apomorphine or any of its ingredients including sodium metabisulfite]
   AND
6. FOR APOKYN REQUESTS: Documentation member has tried and failed (lack of efficacy after reaching the highest tolerated dose for 3 days) or has a labeled contraindication to Kynmobi (apomorphine film)

CONTINUATION OF THERAPY:

A. PARKINSONS DISEASE:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member’s medication fill history (review Rx history for compliance)
   AND
2. Documentation of stabilization or improvement from Apokyn, Kynmobi (apomorphine) therapy as evaluated by a specialist (e.g., an improvement in motor function)
   AND
3. Documentation that the member is still concurrently receiving levodopa or levodopa/carbidopa and adjunctive therapy with anti-Parkinson's agents [e.g., dopamine agonists (pramipexole, ropinirole), Catechol-O-methyl transferase (COMT) inhibitor (entacapone, tolcapone), Monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline)]
   AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified neurologist, or physician who has expertise in movement disorders. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:
Apokyn: Maximum single dose is 0.6 mL (6 mg). Maximum total daily dose is 2ml (20mg).
Only a 1-month supply may be dispensed at a time: 4 cartons of 3-mL cartridges, 5 cartridges per carton (60mL per month).
Kynmobi: Maximum single dose is 30 mg. Do not administer more than 5 doses per day. Only a 1-month supply may be dispensed at a time.

PLACE OF ADMINISTRATION:
The recommendation is that subcutaneous injectable and sublingual medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous, Sublingual

DRUG CLASS:
Non-ergoline Dopamine Receptor Agonists

FDA-APPROVED USES:
Apokyn (apomorphine injection)
Indicated for the acute, intermittent treatment of hypomobility, “off” episodes (“end-of-dose wearing-off” and unpredictable “on-off” episodes) associated with advanced Parkinson disease.
Apokyn has been studied as an adjunct to other Parkinson disease medications.

Kynmobi (apomorphine sublingual film)
Indicated for the acute, intermittent treatment of “off” episodes in patients with Parkinson’s disease

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Hoehn and Yahr Scale
Advanced disease was defined as Stages II to IV of the 5 stage Hoehn and Yahr scale in clinical trials.

Two rating scales are commonly used to stage PD. The Hoehn and Yahr staging scale a was developed and was published in 1967 as a method of designating the severity of Parkinsonism to assess progression and severity of the disease and is still a widely used clinical rating scale. Among its advantages are that it is simple and easily applied. It captures typical patterns of progressive motor impairment which can be applied whether or not patients are receiving dopaminergic therapy. Progression in HY stages has been found to correlate with motor decline, deterioration in quality of life, and neuroimaging studies of dopaminergic loss. However, because of its simplicity and lack of detail, the scale is not comprehensive. It is also limited by its focus on issues of unilateral versus bilateral disease and the presence or absence of postural reflex impairment, thereby leaving other specific aspects of motor deficit unassessed. Also it does not provide any information concerning non-motor aspects of PD. A modified version of HY is sometimes used.

It has five stages: from I (unilateral signs are present) to V (patient confined to a bed or chair unless assisted). The Unified Parkinson's Disease Rating Scale (UPDRS) is a more comprehensive and complex

PD assessment tool. The three main sections of the UPDRS (Mentation, Behavior, and Mood; Activities of Daily Living; and Motor Examination) contain 42 patient interview questions in broad categories, with a higher total score representing worse overall disability (a score of 0 = no disability).

There are other scales for grading the severity of Parkinsonism: The Unified Parkinson's Disease Rating Scale (UPDRS), the modified Columbia Scale, The Webster Scale, The Schwab and England Disability Scale, the Northwestern University Disability Scale and numerous others, each having it's own proponents and usefulness.

The purpose of both the UPDRS and Hoehn and Yahr scale is to provide a snapshot of the patient's condition at the time point at which they are used and are not meant to suggest a timeframe of disease progression. Importantly, the score of the UPDRS can vary within the same patient hour to hour dependent on correlation of medication schedule with the assessment interval.

In Apokyn (apomorphine) clinical trials, 75% of patients were classified as Stage II or III on the Hoehn and Yahr scale, and 22% of the patients were Stage IV.

Hoehn & Yahr Stage	% (n)[1]	Description[3]
II	26.2 (142)	Bilateral involvement but no postural abnormalities
III	49.0 (266)	Bilateral involvement with mild postural imbalance; patient leads independent life
IV	21.9 (119)	Bilateral involvement with postural instability; patient requires substantial help

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Summary of Disease

Parkinson's disease (PD) is a neurologic disease characterized by tremor, rigidity, and bradykinesia. PD is a neurodegenerative disorder caused by a loss of dopaminergic neurons in the substantia nigra, as well as other dopaminergic and non-dopaminergic areas of the brain.1 PD isa common disorder with an estimated prevalence of up to 329 per 100,000. 1 Because PD is progressive and results in significant disability 10 to 15 years after onset, the financial and social burden of PD is substantial, particularly with the aging population.

The cardinal motor features of PD are tremor, bradykinesia, and rigidity.3 Several types of medications are used in the symptomatic treatment of PD, such as levodopa/carbidopa, dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors (e.g., selegiline), amantadine, and anticholinergic agents.B,3 Initial dopaminergic therapy usually provides good control of motor symptoms, but is eventually complicated by motor fluctuations including "off" time (return of PD symptoms when medication effect wears off) and dyskinesia (drug-induced involuntary movements).3 Medications that may be used to reduce off time include entacapone (catechol-O- methyltransferase inhibitor), MAO-B inhibitors, dopamine agonists, and apomorphine.3 Parkinson's disease is a progressive neurodegenerative disorder associated with the loss of dopaminergic cells (cells which produce dopamine) in the substantia nigra region of the brain.

Dopamine is a neurotransmitter that the brain uses to help direct and control movement. In Parkinson's disease, these dopamine producing nerve cells break down, dopamine levels drop, and brain signals directing movement become abnormal. The incidence and prevalence of PD increases with age. The average age of onset is approximately 60 years. Onset in persons younger than 40 years is relatively uncommon. Patients notice symptoms related to progressive bradykinesia (slow movements and reflexes), rigidity, and gait difficulty eventually leading to dementia.

Treatment Goals

There is no cure for Parkinson's disease, however pharmacological agents, physical therapy, and surgical interventions can help control symptoms and improve quality of life. The central objective of using Parkinson's disease medication is to control or manage motor symptoms. There are no established disease-modifying or neuroprotective therapies.[9]

Pharmacologic Agents/Conventional Therapy

There are a wide number of symptomatic treatments that are available for PD, including pharmacological therapy, surgical procedures, physiotherapy, occupational therapy and other support services. All of these treatments can have a significant impact on improving an affected individual's quality of life and should be available. However, despite the increase in non- pharmacological treatments, an individual with Parkinson's becomes more reliant on their medication to maintain their ability to function as the disease progresses. A balance between the side effects of the medication and the benefit often becomes more challenging with time. The current pharmacological treatment options for Parkinson's disease include levodopa/carbidopa, dopamine agonists (bromocriptine, pramipexole, ropinirole), or cathechol-O-methyltransferace (COMT) inhibitors (entacapone, tolcapone). Initial treatments often include low doses of carbidopa/levodopa or a dopamine agonist. Levodopa is still the most effective medication available for treatment of motor symptoms in PD. Patients will eventually need levodopa in their therapeutic regimen as their PD progresses. Levodopa is a first-line medication for PD. The combination of carbidopa and levodopa (Sinemet, Sinemet CR, Parcopa, etc) is the most effective agent available for the treatment of motor symptoms. However, its early use is associated with earlier development of dyskinesias (abnormal involuntary movements). Levodopa-carbidopa (Sinemet, Sinemet CR, Parcopa, etc) can be used first line, especially in elderly patients.

This period of good control lasts approximately five years with levodopa, after which motor fluctuations (e.g., wearing off, on-off phenomenon) and dyskinesias develop. Eventually the drugs are not as effective in many patients since Parkinson's is a progressive disease. Suboptimal control can be managed by increasing the dose of the dopamine agonist or levodopa; however, this approach increases the chance of dopamine agonist side effects (e.g., neuropsychiatric side effects, sedation, sleep attacks).4 It can also cause or worsen dopamine-associated dyskinesias.

As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments. Initial therapy generally becomes less effective and additional motor complications develop, including dyskinesias and motor fluctuations. "On time" refers to the time when medication is effectively controlling the disease's symptoms, and "off time" occurs when disease symptoms recur gradually or abruptly. AsPD progresses, on time becomes shorter, causing complications that can impair quality of life.

Within 4 to 5 years of treatment with standard Parkinson's drug treatments, many patients experience episodes of hypomobility (e.g., inability to rise from a chair, to speak, or to walk). The episodes can occur toward the end of a dosing interval with standard medications (so-called "end-of-dose wearing off") or at unpredictable times (spontaneous "on/off" periods). The intensity, duration and frequency of "off" episodes vary for each patient. Therefore, most clinicians prefer to use a combination of agents rather than increase the dose of a single agent after the initial "honeymoon."

Dopamine agonists are another option for the treatment of PD. These agents act directly on dopamine receptors and are associated with a lower incidence of dyskinesias. There are 2 subclasses of dopamine agonists: Non-ergot-derived agonists (pramipexole and ropinirole); the ergot-derived drugs (bromocriptine, cabergoline, lisuride and pergolide). Apomorphine is not used first-line and is considered in the section 'Adjuvant therapy for more advanced Parkinson's disease', below.

Apokyn (apomorphine) is a non-ergot dopamine agonist indicated for the acute treatment of "off'' episodes associated with advanced PD.

The efficacy of Kynmobi was evaluated in one, randomized, double-blind, placebo-controlled parallel-group study. The study included an open-label titration phase where patients received a starting dose of 10 mg which could be increased on subsequent days in 5 mg increments to a maximum of 35 mg until a full "on" response was achieved and the dose was tolerated. Patients were then randomized to receive the effective dose or placebo in a 12-week double-blind maintenance phase. The primary efficacy endpoint was the in-clinic mean change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part III Score from pre-dose to 30 min post-dose at the 12-week visit. The MDS-UPDRS, Part III Score is designed to assess severity of classic motor findings seen in Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability) with a higher score indicating more severe disease.
The mean change in MDS-UPDRS, Part III Scores from pre-dose to 30 minutes post-dose was statistically significant in the Kynmobi group compared to placebo. (See table below). At week 12, significant differences in MDS-UPDRS, Part III scores from placebo were observed as early as 15 minutes post-dose (first measured time point) and continued up to 90 minutes (last measured time point).
The response rate of self-rated full on response within 30 min at week 12 was 35% in the Kynmobi group vs. 16% in the placebo group (OR 2.81, 95% CI 1.04 to 7.64, p=0.043). The response rate of self-rated full on response within 30 minutes with effect lasting for 30 minutes at week 12 was 31% in patients receiving Kynmobi and 14% in the placebo group (OR 2.80, 95% CI 1.00 to 7.84, p=0.050).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Apokyn (apomorphine) and Kynmobi (apomorphine) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to apomorphine include: Concomitant use of apomorphine with 5HT3 antagonists, including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron, and hypersensitivity to apomorphine, its excipients or sodium metabisulfite.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:
Apokyn SOCT 30MG/3ML
Apomorphine HCl SOCT 30MG/3ML
Kynmobi FILM 10MG (30 EA)
Kynmobi FILM 15MG (30 EA)
Kynmobi FILM 20MG (30 EA)
Kynmobi FILM 25MG (30 EA)
Kynmobi FILM 30MG (30 EA)
Kynmobi Titration Kit KIT 10/15/20/25/30MG (10 EA)

REFERENCES

1. Apokyn (apomorphine) [prescribing information]. Louisville, KY: US World Meds; June 2022
2. KYNMOBI (TM) sublingual film, apomorphine HCl sublingual film. Sunovion Pharmaceuticals Inc (per FDA), Marlborough, MA, September 2022
3. Suchowersky O, Reich S, Perlmutter J, et al. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:968-975.
4. Stowe R, Ives N, Clarke CE, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson's disease patients with motor complications. Cochrane Database Syst Rev. 2010;(7): CD007166.
5. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66(7):983-995.
6. Fox, S. H., Katzenschlager, R., Lim, S., Barton, B., De Bie, R. M., Seppi, K., . . . Sampaio, C. (2018). International Parkinson and movement disorder society evidence-based Medicine Review: Update on treatments for the motor symptoms of parkinson's disease. Movement Disorders, 33(8), 1248-1266. doi:10.1002/mds.27372

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Appendix Contraindications/Exclusions/ Discontinuation Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Required Medical Information FDA Approved Uses	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file