BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

APOKYN® (apomorphine) subcutaneous injection
Apomorphine subcutaneous injection
ONAPGO™ (apomorphine) subcutaneous injection
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for APOKYN (apomorphine)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Neurologist or in consultation with a Neurologist

Indication
- Acute, intermittent treatment of hypomobility, "off" episodes (end-of-dose wearing off and unpredictable on/off episodes) associated with advanced Parkinson's disease

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Age Requirement
- 18 years or older

Baseline Clinical Evaluation
- Parkinson's disease is Hoehn and Yahr Stage 2 or greater during "off" episodes
- At least 2 hours of "off" time per day
- Currently receiving carbidopa/levodopa therapy and will continue

Alternative Therapies
- Failure, contraindication, intolerance to **ALL** the following:
  - One dopamine agonist (e.g., pramipexole or ropinirole)
  - One monoamine oxidase (MOA) B inhibitor (e.g., selegiline or rasagiline mesylate)
  - One catechol O-methylase inhibitor (COMT) (e.g., entacapone or tolcapone)

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents of **generic apomorphine subcutaneous injection** (when available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No severe hepatic impairment (Child-Pugh Class C)
- No severe renal impairment (CrCl less than 15 mL/min) or end-stage renal disease requiring hemodialysis
- No concomitant use with 5HT3 antagonists including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron
- No hypersensitivity to apomorphine, its excipients or sulfite (sodium metabisulfite)

Documentation Requirements
- A completed request form must be submitted, including
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

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Prescriber Qualification
- Continues to be seen by a Neurologist or is in consultation with a Neurologist

Clinical Response
- Positive clinical response defined as **TWO** of the following:
  - Reduced “off” time of at least 1 hour during waking hours
  - Increased “on” time of at least 1 hour
  - Able to perform most activities of daily living
  - No evidence of disease progression

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents of **generic apomorphine subcutaneous injection** (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No severe hepatic impairment (Child-Pugh Class C)
- No severe renal impairment (CrCl less than 15 mL/min) or end-stage renal disease requiring hemodialysis
- No concomitant use with 5HT3 antagonists including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron
- No hypersensitivity to apomorphine, its excipients or sulfite (sodium metabisulfite)
- No development of significant adverse drug effects such as:
  - Hemolytic anemia
  - Impulse control/compulsive behaviors
  - Cardiac or cerebral ischemia
  - QTc prolongation

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

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Medical Necessity Requirements for ONAPGO (apomorphine)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Neurologist or in consultation with a Neurologist

Indication
- Advanced Parkinson's disease with motor fluctuations

Age Requirement
- 18 years or older

Baseline Clinical Evaluation
- Parkinson's disease is Hoehn and Yahr Stage 2 or greater during "off" episodes
- At least 2 hours of "off" time per day
- Currently receiving carbidopa/levodopa therapy and will continue

Alternative Therapies
- Failure, contraindication, intolerance to **ALL** the following:
  - One dopamine agonist (e.g., pramipexole or ropinirole)
  - One monoamine oxidase B inhibitor (e.g., selegiline or rasagiline mesylate)
  - One catechol O-methylase inhibitor (e.g., entacapone or tolcapone)

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No severe hepatic impairment (Child-Pugh Class C)
- No severe renal impairment (CrCl less than 15 mL/min) or end-stage renal disease requiring hemodialysis
- No concomitant use with 5HT3 antagonists including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron
- No hypersensitivity to apomorphine, its excipients or sulfite (sodium metabisulfite)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes

- Lab results
- Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a Neurologist or is in consultation with a Neurologist

Clinical Response

- Positive clinical response defined as **TWO** of the following:
  - Reduced “off” time of at least 1 hour during waking hours
  - Increased “on” time of at least 1 hour
  - Able to perform most activities of daily living
  - No evidence of disease progression

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No severe hepatic impairment (Child-Pugh Class C)
- No severe renal impairment (CrCl less than 15 mL/min) or end-stage renal disease requiring hemodialysis
- No concomitant use with 5HT3 antagonists including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron
- No hypersensitivity to apomorphine, its excipients or sulfite (sodium metabisulfite)
- No development of significant adverse drug effects such as:
  - Hemolytic anemia
  - Impulse control/compulsive behaviors
  - Cardiac or cerebral ischemia
  - QTc prolongation

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Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications
2. Off-Label Use of Cancer Medications

Benefit Type:

Pharmacy Benefit:
Apokyn
Apomorphine
Onapgo

Medical Benefit:
Apokyn
Apomorphine
Onapgo

Coding:

HCPCS: J0364, C9399, J3490

Description:

Apokyn (apomorphine) and generic apomorphine subcutaneous injections are non-ergoline dopamine agonists 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.
Onapgo (apomorphine) solution for subcutaneous infusion is indicated for the treatment of motor fluctuations in adults with advanced Parkinson's disease.

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Motor symptoms of PD are caused by a progressive degeneration of Dopamine (DA) containing neurons in the brain. Non-motor manifestations such as cognitive and psychiatric symptoms are thought to be due to degeneration of other neurotransmitter systems within the brain. Degeneration of the DA neurons leads to DA deficiency and as a result the development of the classic triad of motor symptoms of resting tremor, muscle rigidity and bradykinesia. With the development of DA deficiency, there is also a relative excess of acetylcholine activity.

Drug therapy is targeted at reducing symptoms by enhancing the effects of DA or inhibiting the effects of acetylcholine. Levodopa has been long recognized in clinical practice guidelines and texts as the standard of care for PD. It is a precursor of DA and is able to cross the blood brain barrier where it is converted to DA. Levodopa is thought to be protective against the dopaminergic neuron damage observed in PD. Levodopa is converted to DA in the periphery before it is able to cross the blood brain barrier resulting in gastrointestinal adverse effects and a lower-than-expected concentration of levodopa within the brain. To avoid this, levodopa is combined with carbidopa resulting in a decrease in the peripheral conversion of levodopa to DA and allowing for more levodopa to reach the brain to then be converted to DA. The combination of carbidopa/levodopa is one of the most effective treatments available for symptomatic relief of PD.

In the early stages of levodopa therapy, patients experience a smooth and even response. As PD advances, the effect of levodopa wears off approximately 4 hours after each dose. As many as 50% of patients on levodopa for 5 years, will eventually experience motor fluctuations and dyskinesia. Motor fluctuations are shifts between “on” periods where the patient is responding to levodopa therapy and “off” periods, or end-of-dose effect, where the patient experiences PD symptoms. Dyskinesia consists of a wide range of involuntary movements and typically appears during the patient’s “on” period. These symptoms of motor fluctuations and dyskinesia are commonly seen in patients with early onset (< 50 years of age) PD and are unique to levodopa therapy. For treatment of PD with motor fluctuations and dyskinesia, adjunctive therapy is often necessary to address these complications.

Other treatments for PD include DA receptor agonists, catechol-O-methyltransferase (COMT) inhibitors, selective mono-amine oxidase type-B (MAOI-B) inhibitors, an adenosine receptor antagonist (istradefylline), amantadine, and selective use of anticholinergic agents. These agents are effective and safe in controlling motor symptoms in patients with advanced PD when used as adjunctive treatment to Levodopa. There is insufficient evidence to conclude that any one of these medications is clinically superior to another and there is insufficient evidence that shows one PD medication as superior to another in terms of improvement in functional outcomes.

On-demand rescue strategies for prolonged “off” periods can occur despite maintenance therapy. Apomorphine sublingual film and subcutaneous injections and inhaled levodopa are available for on-demand therapy.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Hoehn and Yahr Scale and the Modified Hoehn and Yahr Scale:

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
0	No signs of disease	No signs of disease

1	Unilateral involvement only, usually minimal or no functional disability	Unilateral involvement only
1.5	--	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	--	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severely disability; still able to walk or stand unassisted
5	Confined to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided
Hoehn M, Yahr M: Parkinsonism: onset, progression and mortality. Neurology 1967; 17 (5):427-442		

Oral Anti-Parkinson's disease agents	
Carbidopa	Carbidopa generic tabs Lodosyn tabs
Carbidopa+Levodopa	Carbidopa+Levodopa – immediate release generic tabs Carbidopa+Levodopa ER – extended-release generic tabs Carbidopa+Levodopa ODT generic tabs Crexont – extended release caps Dhivy – immediate release tabs Duopa – enteral suspension Rytary – extended-release caps Sinemet – immediate release tabs Sinemet CR – extended-release tabs
Carbidopa+Levodopa+Entacapone	Carbidopa+Levodopa+Entacapone generic tabs Stalevo tabs
Levodopa	Inbrija – oral inhalation
Foslevodopa/Foscarbidopa	Vyalev – IV pump
COMT inhibitors	Entacapone generic tabs Comtan (entacapone) tabs Tolcapone generic tabs Tasmar (tolcapone) tabs Ongentys (opicapone)
DA agonists	Bromocriptine generic tabs Parlodel (bromocriptine) tabs Pramipexole – immediate release generic tabs Pramipexole ER – extended-release generic tabs Mirapex (pramipexole) – immediate release tabs Mirapex ER (pramipexole) – extended-release tabs Ropinirole – immediate release generic tabs Ropinirole ER – extended-release generic tabs Requip (ropinirole) – immediate release tabs Requip XL (ropinirole) – extended-release tabs

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MAO-B inhibitors	Rasagiline generic tabs Azilect (rasagiline) tabs Xadago (safinamide) tabs Selegiline generic tabs and caps Eldepryl (selegiline) caps Zelapar (selegiline) – ODT tab
Adenosine receptor antagonist	Nourianz (istradefylline) tabs
Anticholinergic agents for PD	Benztropine Diphenhydramine Trihexyphenidyl

Resources:

Apokyn (apomorphine) product information, revised by MDD US Operations, LLC 10/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed March 6, 2025.

Apomorphine product information, revised by TruPharma, LLC 02/2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 5, 2025.

Chou KL. Clinical manifestations of Parkinson disease. In: UpToDate, Hurtig HI, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2025. Topic last updated March 14, 2024. Accessed April 4, 2025.

Liang TW. Medical management of motor fluctuations and dyskinesia in Parkinson disease. In: UpToDate, Hurtig HI, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2025. Topic last updated March 4, 2025. Accessed April 4, 2025.

Onapgo (apomorphine) product information, revised by MDD US Operations, LLC, a subsidiary of Supernus Pharmaceuticals, Inc 10/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed March 6, 2025.

Spindler MA. Initial pharmacologic treatment of Parkinson disease. In: UpToDate, Hurtig HI, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2025. Topic last updated January 21, 2025. Accessed April 4, 2025.