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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119



Prior Authorization Criteria Update: omaveloxolone (SKYCLARYS) capsules

Plain Language Summary:

- SKYCLARYS (omaveloxolone) is the first medicine approved in the United States to treat Friedreich's ataxia (FDRA). Omaveloxolone is indicated for the treatment of FDRA in adults and adolescents aged 16 years and older.
- Friedreich's ataxia is a rare, inherited disease that causes damage to the nervous system and decreases the length of life of people with this condition. People with FDRA have unsteady balance, muscle weakness and it becomes harder to walk, dress, and speak as time goes on.
- The main goals of therapy are to treat the symptoms and provide support.
- In one study, omaveloxolone mildly improved muscle coordination in people with FDRA.
- Omaveloxolone may increase liver function tests. These changes in test results were temporary and returned to normal when omaveloxolone was discontinued. Other side effects seen from people in the study were nausea, headache, stomach pain, diarrhea, and feeling tired.
- Neurologists who prescribe omaveloxolone to a person enrolled in the Oregon Health Plan (OHP) must receive approval from Oregon Health Authority before the OHP will pay for it. This process is called prior authorization (PA).

Purpose of Update: Review evidence for omaveloxolone and amend the current PA criteria to provide a clinically appropriate pathway to coverage for eligible Oregon Health Plan (OHP) fee-for-service members with FDRA.

Background:

Friedreich's ataxia is a rare, progressive, autosomal recessive, neurodegenerative disorder. It is the most common hereditary ataxia in people of Western European descent.¹ Mutations in the frataxin gene on chromosome 9 are the primary cause of FDRA. Frataxin is a protein that is essential for mitochondrial function and mitochondrial iron metabolism. The mutations arise from repeats of guanine-adenine-adenine DNA sequences within the frataxin gene that causes a deficiency of frataxin. That shortage leads to the degeneration of nerve cells that adversely impacts muscle coordination.¹ The guanine-adenine-adenine repeats that cause FDRA are most commonly found in individuals of European, North African, Middle Eastern, or Indian descent.¹ As a result, the prevalence of the disease is lowest in China, Japan and sub-Saharan Africa.¹ The estimated prevalence of FDRA ataxia in European populations is 1 in 50,000.² In the United States, prevalence is approximately 1 in 5,000 people.³ In 2023, approximately 30 people enrolled in the OHP had FDRA, of which most received health care through a coordinated care organization (CCO).

Friedreich's ataxia presents as impaired coordination of both arms and legs, loss of normal reflexes in the ankles and knees, vision and hearing loss, slurred speech, scoliosis, and increased spasticity.² The onset of symptoms is usually between the ages of 5 and 15 years.² Symptoms will continue to progress with increasing difficulty in balance, gait, and activities of daily living (i.e., writing, dressing, washing and feeding).² Age of onset is an important predictor of disease severity and the speed of disease progression.⁴ Children diagnosed with early onset FDRA before 7 years of age tend to have more genetic mutations and severe symptoms that rapidly progress to impaired neuromuscular abilities.⁴ Skeletal deformities and cardiomyopathy are found in most people with FDRA, and many also have increased frequency of impaired glucose tolerance and diabetes.² Most people with early-onset FDRA will be wheelchair-dependent by their late teens

or early twenties.² The mean age of death is 37.5 years, although some people with late-onset FDRA (after 25 years of age) have survived until they reached 80 years of age.¹ The major cause of death is congestive heart failure or cardiac arrhythmia.^{5,6}

The diagnosis of FDRA is based upon clinical findings and confirmed by genetic testing.¹ Neuroimaging of the brain and spinal cord is recommended to exclude other causes of ataxia.¹ The neurological-exam-based Friedreich's Ataxia Rating Scale (FARS) was developed to assess the severity of ataxia symptoms.⁷ The maximum score is 125 points, based five sections that measure 1) bulbar function (score 0 to 11); 2) upper limb coordination (score 0 to 36); 3) lower limb coordination (score 0 to 16); 4) peripheral nervous system function (score 0 to 26); and 5) upright stability (score 0 to 36).^{7,8} The interrater reliability of this tool was verified in 3 studies of patients with FDRA.⁹⁻¹¹ However, the minimal clinically important difference (MCID) for this assessment was never defined.¹¹ An assessment of the ability to complete activities of daily living (ADL) is part of the FARS scoring.⁷ The FARS-ADL is a 9-question assessment which assesses 9 abilities: speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function.⁷ Each component is scored between 0 and 4, with 0 being normal and 4 being worst.⁷

The modified FARS (mFARS) is another clinical assessment tool used to assess patient function and includes 4 of the 5 sections of the FARS: bulbar function, upper limb coordination, lower limb coordination, and upright stability.³ Peripheral nervous system function is not measured in the mFARS scoring. The minimum score is 0 and the maximum score is 99.³ A lower score indicates better neurological function and less physical impairment.³ A reduction in FARS or mFARS signifies improved functioning.⁷ An MCID for the mFARS has also not been determined. However, in a 5-year natural history study that included over 800 patients aged 4 to 80 years with FDRA, the mean progression in mFARS scores from baseline was 1.9 points by year one, 4.2 points by year 2, and 9.6 points by year 5.¹⁰

Management of FDRA is palliative and focused on symptomatic support from physical therapy, cardiology, endocrinology, neurology, and orthopedics to maintain optimal functioning as long as possible.¹ Until the Food and Drug Administration (FDA) approval of omaveloxolone, no medication had been approved to treat FDRA. Omaveloxolone is indicated for the treatment of FDRA in adults and adolescents aged 16 years and older.¹² Omaveloxolone oral capsules received FDA approval in February 2023 with priority review under orphan drug status and rare pediatric disease designation.³ The FDA-approved label for omaveloxolone states the "precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown."¹² The label goes on to say that omaveloxolone activates a nuclear factor pathway that is involved in the cellular response to oxidative stress and restores mitochondrial function in fibroblasts obtained from patients with FDRA.¹²

The evidence for the FDA-approval of omaveloxone was reviewed by the Pharmacy and Therapeutics Committee at the June 2023 meeting and is summarized in the following paragraphs. The efficacy and safety of omaveloxolone to slow the progression of FDRA were evaluated in a multi-center, placebo-controlled, double-blind, Phase 2 randomized trial (MOXIe) in patients aged 16 to 40 years of age with genetically confirmed FDRA.³ Eligible patients had stable baseline mFARS scores between 20 and 80, could complete maximal exercise testing on a recumbent stationary bicycle, and had a left ventricular ejection fraction of 40% or greater.³ The mFARS scores represented individuals just after time of presentation with FDRA in its mildest form. Most of the patients (92%) were ambulatory. Patients with uncontrolled diabetes (HbA1c > 11%), significant cardiac disease (i.e., left-sided heart disease), active infection, clinically significant hepatic disease, and significant laboratory abnormalities (e.g., B-type natriuretic peptide [BNP] > 200 pg/mL) were excluded from the study. Ability to ambulate was not part of the exclusion criteria.

A total of 103 patients were randomized in a 1:1 ratio to omaveloxolone oral 150 mg once daily or matched placebo. Of the patients enrolled in the study, 53% were male, 97% were white, and the mean age was 24 years at study entry.³ The primary outcome was change in mFARS from baseline at 48 weeks.³

Improvement was defined by the investigators as an increase of no more than 1.9 points in mFARS score from baseline based upon previous studies that demonstrated an average decline of 1 to 2 points per year in the FARS clinical rating scale.³ At 48 weeks, low-quality evidence showed mean mFARS scores (scale 0 to 99) improved by 1.55 points in the omeveloxolone group and decreased by 0.85 points in the placebo group (mean difference between groups -2.4 points; 95% confidence interval [CI] -4.3 to -0.5; p=0.014).³ The clinical significance of a 2.4-point difference for a 99-point scale is unclear. The primary efficacy analysis was based on a full analysis set, which consisted of 82 patients without pes cavus (loss of lateral support, determined by visualization of light from a flashlight under the foot arch when barefoot and weight bearing).³ Presence of pes cavus may affect people's ability to use their legs, walk, and perform neurologic testing independent of their ataxia.

In an open-label extension study, 73 patients from the full analysis set of the MOXIe trial either continued on omeveloxolone, or switched to omeveloxolone from placebo (i.e., delayed-start).¹³ The difference in mFARS between omeveloxolone and placebo observed at the end of the MOXIe trial (week 48) was preserved at the end of the delayed-start period (extension week 72).¹³ The noninferiority testing demonstrated that the difference in mFARS between omeveloxolone and placebo observed at the end of placebo-controlled MOXIe part 2 (-2.17 ± 1.09 points) was preserved after 72 weeks in the extension (-2.91 ± 1.44 points).¹³ Additionally, patients previously randomized to omeveloxolone in the MOXIe trial maintained mean mFARS values from extension baseline through 144 weeks.¹³ The longer-term safety profile of omeveloxolone in the extension study was similar to that seen in MOXIe Parts 1 and 2, and omeveloxolone was generally well tolerated in the extension study.¹³ Serious adverse events were reported in 13 (8.7%) patients; of these, 8 (7.5%) individuals were in the placebo-omeveloxolone group and 5 (11.6%) were in the omeveloxolone-omeveloxolone group.¹³

The most common adverse effects of omeveloxolone observed in clinical trials with omeveloxolone compared with placebo were transient increases in alanine transaminase (ALT) and aspartate aminotransferase (AST) (37% vs. 2%), headache (37% vs. 25%), nausea (33% vs. 13%), abdominal pain (29% vs. 6%), fatigue (24% vs. 14%), diarrhea (20% vs. 10%) and musculoskeletal pain (20% vs. 15%).¹² In part 2 of the MOXIe trial, increases in B-type natriuretic peptide (BNP) above the upper limit of normal (100 pg/mL) were observed in 14% of omeveloxolone-treated patients (compared with 4% of placebo-treated patients).³ The manufacturer recommends obtaining ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating treatment and periodically during treatment.¹²

Omeveloxolone is contraindicated in patients with severe hepatic impairment. The omeveloxolone dose should be adjusted to 100 mg once daily in patients with moderate hepatic impairment.¹² Due its hepatic metabolism by CYP3A4 enzymes, there are numerous drug interactions between omeveloxolone and other medications. The omeveloxolone dose should be adjusted to 50 or 100 mg once daily when co-administered with strong or moderate CYP3A4 inhibitors, respectively.¹²

Recommendation: Amend clinical PA criteria to include prescribing by a neurologist, add genetic confirmation of FDRA, and remove requirement for patients to be ambulatory.

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Appendix 1. Proposed Prior Authorization Criteria

Omaveloxolone (SKYCLARYS™)

Goal(s):

Promote use that is consistent with medical evidence and product labeling in patients with Friedreich’s ataxia.

Length of Authorization:

- Up to 12 months

Requires PA:

- Omaveloxolone oral capsules (pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Recommended Dosage of Omaveloxolone with Concomitant use of CYP3A4 Inhibitors or Inducers

Concomitant Drug Class	Dosage
Strong CYP3A4 Inhibitor (such as, but not limited to: ketoconazole, nefazodone, voriconazole)	Recommended to avoid concomitant use. If co-administration cannot be avoided: <ul style="list-style-type: none">• Reduce omaveloxolone dose to 50 mg once daily with close monitoring to detect adverse effects• If adverse effects emerge, coadministration with strong CYP3A4 inhibitor should be discontinued
Moderate CYP3A4 Inhibitor (such as, but not limited to: erythromycin, verapamil, diltiazem, cyclosporine)	Recommended to avoid concomitant use. If co-administration cannot be avoided: <ul style="list-style-type: none">• Reduce omaveloxolone dose to 100 mg once daily with close monitoring to detect adverse effects• If adverse effects emerge, further reduce omaveloxolone dose to 50 mg once daily
Strong or Moderate CYP3A4 Inducer (such as, but not limited to: phenytoin, carbamazepine, rifampin)	Recommended to avoid concomitant use.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the medication prescribed by or in consultation with a neurologist?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for a patient who has had a trinucleotide repeat expansion assay genetic test confirming the diagnosis of Friedreich's ataxia in a patient 16 years of age and older?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Is the patient able to swallow whole capsules or capsule contents mixed into an appropriate amount of applesauce? Note: Capsules should be swallowed whole or mixed into 30 mL of applesauce. Capsule contents should not be mixed with milk, orange juice, or given via enteral feeding tube. Capsules may not be crushed or chewed.	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Have baseline labs (alanine transaminase [ALT], aspartate aminotransferase [AST], bilirubin, b-type natriuretic peptide [BNP] and lipid parameters) been obtained prior to initiating therapy?	Yes: Document date and results: Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Is baseline BNP > 200 pg/mL?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #8
8. Has the provider documented the patient does not have severe hepatic impairment (Child-Pugh Class C)?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. If patient has moderate liver impairment (Child-Pugh Class B) has the dose been modified to 100 mg once daily?	Yes: Go to #10	No: Pass to RPh. Deny; medical appropriateness
10. If patient is taking other medications, are they CYP3A4 inhibitors or inducers that require omaveloxolone dosing adjustments as outlined in Table 1 and has the omaveloxolone dose been adjusted?	Yes: Approve for up to 6 months.	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition progressed slower than expected, stabilized, or improved as assessed by the prescribing provider and provider attests to patient's current status.	Yes: Approve for 12 months. Document baseline assessment and provider attestation received.	No: Pass to RPh; Deny; medical appropriateness.

*P&T/DUR Review: 2/25 (DM); 6/23 (DM)
Implementation: 3/10/25; 7/1/23*