09-J4000-49

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Reviewed: 11/12/25

Revised: 12/15/25

Subject: Omaveloxolone (Skyclarys) Oral Capsule

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Friedreich's ataxia (FA) is a rare autosomal recessive neurodegenerative disease caused by a biallelic trinucleotide (GAA) repeat expansion in intron 1 of the *FXN* gene on chromosome 9. It is the most common hereditary ataxia, affecting an estimated 1 in 50,000 people in the United States with a strong prevalence among those of European ancestry. FA patients have about 66 to 1,700 GAA triplets, which cause transcription errors and lead to a deficiency of frataxin. Frataxin is concentrated in neuronal tissue and is needed for mitochondrial function. A deficiency of frataxin results in intramitochondrial iron accumulation, defective mitochondrial respiration, excessive oxygen free radical production, and ultimately a loss of sensory fibers. Patients typically present with FA in their early to mid-teen years with an initial complaint of gait instability which progresses to cerebellar ataxia, sensory loss, muscle weakness, dysarthria, dysphagia, cardiomyopathy, metabolic complications, and urological dysfunction. Loss of these aforementioned functions results in impaired activities of daily living, as the mean time to wheelchair dependence is approximately 10 years from diagnosis. Additionally, the mean age of death is 37 years, with cardiac abnormalities causing a majority of premature deaths.

FA patients are typically diagnosed based on genetic testing and clinical presentation. Patients are evaluated using a variety of assessment tools including, but not limited to, the Scale for Assessment and Rating of Ataxia (SARA), Inventory of Non-Ataxia Symptoms, and spinocerebellar functional index. Until recently, treatment was symptomatic management and tailored based on the patient's needs (e.g., occupational therapy). On February 28, 2023, the FDA approved omaveloxolone (Skyclarys), a once-daily oral nuclear factor erythroid 2-related factor 2 (Nrf2) activator, for the treatment of FA in adults and adolescents 16 years of age and older. Omaveloxolone is believed to improve mitochondrial function in that the Nrf2 pathway is involved in the cellular response to oxidative stress.

The efficacy and safety of omaveloxolone (Skyclarys) was evaluated in the MOXIe Study Part 1, Part 2

and an open-label extension study. The MOXIe Study Part 1 was a phase II, double-blind, randomized, placebo-controlled, dose-ranging, multi-center study of omaveloxolone in FA patients. Patients' mean age was 25.6 years and at diagnosis was 15.3 years. Ninety percent of patients were ambulatory with a mean modified Friedreich's Ataxia Rating Scale (mFARS; maximum total score is 93 with higher scores equating to greater disease severity) score of 41.1. Patients (n = 69) were randomized 3:1 to either omaveloxolone (dose range: 2.5–300 mg/day) or placebo administered once daily for 12 weeks. Based on changes in ferritin and GGT, omaveloxolone's (Skyclarys) optimal doses were 80 mg and 160 mg daily. No significant changes were observed in the primary outcome of peak workload in maximal exercise testing (p = 0.77 versus placebo for all omaveloxolone dose groups). However, omaveloxolone (Skyclarys) 160 mg daily did improve the secondary outcome of the mFARS by 3.8 points versus baseline (p = 0.0001) and by 2.3 points versus placebo (p = 0.06). The most frequent adverse effects associated with omaveloxolone as compared to placebo included upper respiratory tract infection (40% versus 6%), nasopharyngitis (14% versus 0%), diarrhea (12% versus 6%), increase in alanine aminotransferase (12% versus 0%), increase in aspartate aminotransferase (12% versus 0%), nausea (10% versus 6%) and arthralgia (10% versus 0%).

The MOXIe Study Part 2 was a phase II international, double-blind, randomized, placebo-controlled, parallel-group study at 11 facilities in the United States, Europe, and Australia. Inclusion criteria consisted of patients 16 to 40 years of age with genetically confirmed FA and a baseline modified Friedreich's Ataxia Rating Scale (mFARS) scores between 20 and 80. One hundred three patients were randomized 1:1 to placebo (n = 52) or omaveloxolone 150 mg daily (n = 51). The primary outcome was change from baseline in the mFARS score at 48 weeks. The efficacy analysis was performed for 40 patients in the omaveloxolone arm and 42 patients in the placebo arm. Changes from baseline in mFARS scores in omaveloxolone (−1.55 ± 0.69) and placebo (0.85 ± 0.64) patients showed a difference between treatment groups of –2.40 ± 0.96 (p = 0.014). Adverse effects occurred more frequently with omaveloxolone as compared to placebo and included transient, reversible increases in aminotransferase levels (37% versus 2%), headache (37% versus 25%), nausea (33% versus 14%), and fatigue(22% versus 14%).

The MOXIe open-label extension study followed 75 patients (39 previously on placebo and 34 previously on omaveloxolone) from the MOXIe Part 2. All patients in the extension study received omaveloxolone (Skyclarys) 150 mg daily. The primary objective was to compare mFARS scores at the end of MOXIe Part 2 with those at 72 weeks of the extension and up to 144 weeks for patients who received omaveloxolone throughout Part 2. Noninferiority testing demonstrated that the difference in mFARS between omaveloxolone (Skyclarys) and placebo observed at the end of Part 2 (–2.17 ± 1.09 points) was preserved after 72 weeks in the extension (–2.91 ± 1.44 points). Additionally, patients who received omaveloxolone throughout Part 2 showed no worsening in mFARS relative to their extension baseline through 144 weeks.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital,

ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of omaveloxolone (Skyclarys) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member is 16 years of age or older with a diagnosis of Friedreich's ataxia.
2. Member has a genetic test demonstrating biallelic pathogenic variants in the *FXN* gene. – Laboratory documentation of the genetic testing results must be submitted.
3. Member has early stage disease with meaningful voluntary motor function (e.g., manipulate objects using upper extremities, ambulates).
4. Member does not have severe hepatic impairment (i.e., Child-Pugh Class C).
5. Member has a B-Type Natriuretic Peptide (BNP) is less than or equal to 200 pg/mL and no clinically significant cardiac disease (Note: Does not include mild-to-moderate cardiomyopathy associated with FA).
6. The medication is prescribed by, or in consultation with, a neurologist, neuromuscular specialist, or geneticist.
7. The dose does not exceed 150 mg orally daily.

Approval duration: 6 months

Continuation of omaveloxolone (Skyclarys) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met all indication-specific initiation criteria.
2. The member has had a clinical meaningful response (i.e., improvement, stabilization of disease, or slowed progression) with no significant adverse drug reactions (e.g., heart failure, liver failure) necessitating discontinuation of therapy.
3. The medication is prescribed by, or in consultation with, a neurologist, neuromuscular specialist, or geneticist.
4. The dose does not exceed 150 mg orally daily.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Omaveloxolone (Skyclarys) is indicated for the treatment of Friedreich's ataxia in adults and

adolescents aged 16 years and older.

- The recommended omaveloxolone (Skyclarys) dosage is 150 mg (3 capsules) taken orally once daily.
- Administer omaveloxolone (Skyclarys) on an empty stomach at least one hour before eating.
- Omaveloxolone (Skyclarys) capsules should be swallowed whole. Do not open, crush or chew.

Dose Adjustments

- Dosage adjustments are recommended when omaveloxolone (Skyclarys) is administered with a strong or moderate CYP3A4 inducer or inhibitor medication (Table 1) and for patients with hepatic impairment (Table 2).

Table 1: Recommended Dosage of Omaveloxolone (Skyclarys) with Concomitant Use of CYP3A4 Inhibitors and Inducers

Concomitant Drug Class	Dosage
Strong CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of omaveloxolone (Skyclarys) to 50 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, coadministration with strong CYP3A4 inhibitors should be discontinued.
Moderate CYP3A4 inhibitor	Recommended to avoid concomitant use. If coadministration cannot be avoided: • Reduce the dosage of omaveloxolone (Skyclarys) to 100 mg once daily with close monitoring for adverse reactions. • If adverse reactions emerge, further reduce the dosage of omaveloxolone (Skyclarys) to 50 mg once daily
Strong or Moderate CYP3A4 inducer	Recommended to avoid concomitant use.

Table 2: Recommended Dosage of Omaveloxolone (Skyclarys) in Patients with Hepatic Impairment

Impairment Classification (Child-Pugh)	Dosage
Severe (Child-Pugh Class C)	Avoid use
Moderate (Child-Pugh Class B)	• 100 mg once daily with close monitoring for adverse reactions • Consider lowering to 50 mg once daily if adverse reactions emerge

Mild (Child-Pugh Class A)	150 mg once daily

Drug Availability

- Omaveloxolone (Skyclarys) is supplied as 50 mg capsules and packaged in bottles that contain 90 capsules (NDC 73179-250-90).

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Elevation of Aminotransferases:** Treatment with omaveloxolone (Skyclarys) can cause an elevation in hepatic transaminases (ALT and AST); therefore, monitor ALT, AST, and total bilirubin prior to initiation, every month for the first 3 months of treatment, and periodically thereafter. In clinical trials maximum increases in ALT and AST occurred within 12 weeks after starting therapy and were generally asymptomatic and reversible following discontinuation of omaveloxolone (Skyclarys). If transaminases increase to levels greater than 5 times the ULN, or greater than 3 times the ULN with evidence of liver dysfunction (e.g., elevated bilirubin), immediately discontinue omaveloxolone (Skyclarys) and repeat liver function tests as soon as possible. If transaminase levels stabilize or resolve, omaveloxolone (Skyclarys) may be reinitiated with an appropriate increased frequency of monitoring of liver function.
- **Elevation of B-type Natriuretic Peptide (BNP):** Treatment with omaveloxolone (Skyclarys) can cause an increase in BNP, a marker of cardiac function; therefore, check BNP prior to initiation of omaveloxolone (Skyclarys) and advise patients of signs and symptoms of fluid overload such as sudden weight gain (3 pounds or more of weight gain in one day, or 5 pounds or more of weight gain in a week), peripheral edema, palpitations, and shortness of breath. In clinical trials patients were excluded from if they had BNP levels > 200 pg/mL prior to study entry, or a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with FA. It is unclear whether the elevations in BNP are related to omaveloxolone (Skyclarys) or cardiac disease associated with FA. Elevations in BNP may indicate cardiac failure and should prompt an evaluation of cardiac function. If signs and symptoms of fluid overload develop, worsen, or require hospitalization, evaluate BNP and cardiac function, and manage appropriately. Management of fluid overload and heart failure may require discontinuation of omaveloxolone (Skyclarys).
- **Lipid Abnormalities:** Treatment with omaveloxolone (Skyclarys) can cause changes in cholesterol; therefore, monitor cholesterol prior to initiation and periodically during treatment. If lipid abnormalities occur, manage according to clinical guidelines.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G11.11	Friedreich's Ataxia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Modified Friedreich's Ataxia Rating Scale (mFARS): An assessment rubric specially developed for FA to evaluate neurological function. Based on the neurological examination, functions from 4 domains (i.e., bulbar, upper limbs, lower limbs, upright stability) are assessed with 18 items [i.e., cough (2), speech (3), finger-finger (6), nose-finger (8), dysmetria (8), rapid movements (6), finger taps (8), heel shin slide (8), heel shin tap (8), sitting position (4), stance feet apart (4), stance feet apart-eyes closed (4), stance feet tog (4), stance feet tog-eyes closed (4), tandem stance (4), stance dom. foot (4), tandem walk (3), gait (5)]. Maximum scores per function are noted in brackets and yield a maximum potential total score of 93. The higher scores equate to greater disease severity.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2025. URL www.clinicalpharmacilogy-ip.com Accessed 10/28/25.
2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2023. URL http://www.dynamed.com. Accessed 4/26/23.
3. Lynch DR, Chin MP, Boesch S, et al. Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. *Mov Disord*. 2023;38(2):313-320. doi:10.1002/mds.29286.
4. Lynch DR, Chin MP, Delatycki MB, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). *Ann Neurol*. 2021;89(2):212-225. doi:10.1002/ana.25934.
5. Lynch DR, Farmer J, Hauser L, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Transl Neurol*. 2018;6(1):15-26. Published 2018 Nov 10. doi:10.1002/acn3.660.
6. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 10/28/25.
7. Skyclarys (omaveloxolone) [package insert]. Reata Pharmaceuticals, Inc., Plano (TX): December 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

07/01/23	New Medical Coverage Guideline – Omaveloxolone (Skyclarys) for the treatment of genetically confirmed Friedreich's ataxia in patients 16 years of age and older with early-stage disease.
12/15/23	Review and revision of the guideline, consisting of updating the references.
12/15/24	Review and revision of the guideline, consisting of revising the position statement to require only laboratory documentation for genetic testing and updating the references.
12/15/25	Review and revision of the guideline, consisting of revising the position statement to allow in consultation with a specialist for prescribing and updating the references.