BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

SKYCLARYS™ (omaveloxolone) 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 SKYCLARYS (omaveloxolone)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in Friedreich's ataxia or in consultation with a Neurologist

Indication
- Diagnosis of symptomatic genetically confirmed Friedreich's ataxia

Age Requirement
- 16 years of age or older

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Baseline Clinical Evaluation

- Stable modified Friedreich's Ataxia Rating Scale (mFARS) score between 20 and 80
- Loss of function mutations in the frataxin (FXN) gene located on chromosome 9q13
- Alanine aminotransferase, aspartate aminotransferase, and bilirubin
- B type natriuretic peptide (BNP)
- Lipid panel
- Left ventricular ejection fraction is at least 40 percent

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if 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 concomitant use of:
  - Moderate or strong inducers of CYP3A4 (e.g., dexamethasone, bosentan, carbamazepine, phenytoin, rifampin, etc.)
  - Hormonal contraceptives (pills, patch, ring), implants, and progestin only pills
- Does not have any of the following:
  - Severe hepatic impairment Child Pugh Class C
  - B type natriuretic peptide (BNP) value greater than 200 pg/mL
  - History of clinically significant left sided heart disease and/or clinically significant cardiac disease

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (mFARS score, FXN mutation confirmation, liver enzymes, BNP, lipid panel, ejection fraction)
  - 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 physician specializing in Friedreich's ataxia or is in consultation with a Neurologist

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Clinical Response
- Achieved and maintains **BOTH** of the following:
  - Decrease in the mFARS score of at least 2 points from baseline
  - Instrumental and self care activities of daily living

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if 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 significant adverse drug effects such as:
  - Severe hepatotoxicity
  - Sudden weight gain (e.g., 3 pounds or more in a day or 5 pounds or more in a week), or other signs and symptoms of severe fluid overload that develop, worsen, or require hospitalization
- No concomitant use of:
  - Moderate or strong inducers of CYP3A4 (e.g., dexamethasone, bosentan, carbamazepine, phenytoin, rifampin, etc.)
  - Sensitive substrates for cytochrome CYP2C8 or CYP3A4 (e.g., repaglinide, midazolam, sildenafil, etc.)
  - Substrates for p glycoprotein transporter (e.g., ambrisentan, digoxin, cyclosporine, tacrolimus, etc.)
  - Hormonal contraceptives (pills, patch, ring), implants, and progestin-only pills
- Does not have any of the following:
  - Severe hepatic impairment Child Pugh Class C
  - B type natriuretic peptide (BNP) value greater than 200 pg/mL
  - History of clinically significant left sided heart disease and/or clinically significant cardiac disease

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in Friedreich's ataxia
- Lab values that confirm safe use (mFARS score, BNP, liver enzymes, etc.)

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

ORIGINAL EFFECTIVE DATE: 05/18/2023 | ARCHIVE DATE: | LAST REVIEW DATE: 05/21/2026 | LAST CRITERIA REVISION DATE: 05/15/2025

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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

Description:

Skyclarys (omaveloxolone) is indicated for the treatment of Friedreich's ataxia (FRDA) in adults and adolescents aged 16 years and older. The precise mechanism by which omaveloxolone exerts its therapeutic effect in individuals with FRDA is unknown. Omaveloxolone has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in cellular response to oxidative stress.

A feature of FRDA is impairment of antioxidative defense mechanisms, which play a major role in disease progression. Studies have demonstrated that Nrf2 signaling is grossly impaired in individuals with FRDA. The ability of omaveloxolone to activate Nrf2 and induce antioxidant target genes is hypothesized to be therapeutic in patients with FRDA.

FRDA is an autosomal recessive cerebellar ataxia caused by recurring expansions of a nucleotide triplet. The causative mutation is a repetition of a guanine-adenine-adenine (GAA) triplet in the first intron of the frataxin gene, leading to decreased transcription of frataxin. Frataxin is a mitochondrial protein whose normal role includes iron-sulfur cluster biogenesis, iron chaperoning, iron detoxification, antioxidation, and possibly the regulation of iron storage. It is also thought to play a role in ATP production. With frataxin deficiency there is severe disruption of iron-sulfur cluster biosynthesis, cellular deregulation of iron, mitochondrial iron overload, and an increased sensitivity to oxidative stress.

FRDA is the most common hereditary ataxia. It accounts for up to one-half of hereditary ataxia cases overall, and up to three-quarters of cases among individuals < 25 years of age. It occurs with a frequency of approximately 1 in 30,000 to 1 in 50,000 in Caucasian individuals. Approximately 1 in 100 people carry a mutant copy of FXN.

The GAA triplet repeat expansion that causes FRDA is found only in individuals of European, North African, Middle Eastern, or Indian origin. The prevalence of the disease is lowest in China, Japan, and sub-Saharan Africa.

The major clinical manifestations of FRDA are neurologic dysfunction, cardiomyopathy, and diabetes mellitus. Hypertrophic cardiomyopathy (HCM) is the most common cardiac complication of FRDA, affecting up to 85% of individuals by early adulthood. Overt diabetes mellitus or impaired glucose tolerance occurs in 8 to 32% of individuals with FRDA, which is several times higher than in age-matched controls.

The manifestations of FRDA vary in part with the number of GAA repetitions. The number of GAA repeats can vary in length. Severity of disease and rate of progression are variable, with more severe disease being associated with a higher number of GAA repeats. Higher GAA repetitions, also correlate with earlier age at onset,

shorter time to loss of ambulation, greater frequency of cardiomyopathy, and loss of reflexes in the upper limbs. Individuals with late-onset cerebellar ataxia who have retained reflexes tend to have smaller repeats.

The age of onset of FRDA is usually in the adolescent years but can range from 2 to >70 years of age. Age of onset is an important predictor of overall disease severity and speed of progression with the rate of disease progression varying inversely with the age of onset. With late-onset FRDA, disease progression is generally slower. Age of onset also correlates with number of GAA repeats, with disease onset occurring 2.3 to 2.7 years earlier for every 100 repeats.

Based on a longitudinal study on the natural history of 1100 individuals with FRDA, four onset types have been proposed:
●Early onset (0-7 years) – 324 individuals (29%), median of 790 GAA repeats
●Typical onset (8-14 years) – 438 individuals (39%), median of 704 GAA repeats
●Intermediate onset (15-24 years) – 234 individuals (21%), median of 500 GAA repeats
●Late onset (≥ 25 years) – 119 individuals (11%), median of 250 GAA repeats

In most symptoms begin between 5-15 years. The mean time from symptom onset to use of a wheelchair ranges from 11-25 years. The major cause of death is cardiac dysfunction from congestive heart failure or arrhythmia. Most individuals die between the ages of 30-40 (mean 37 years). Some individuals survive until the eighth decade.

The diagnosis of FRDA is based upon clinical findings, confirmed by genetic testing for the triplet repeat expansions in the first intron of the frataxin (FXN) gene that causes FRDA.

Treatment of FRDA involves managing specific symptoms of the disease. There is no specific disease-modifying therapy for FRDA.

Definitions:

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

Reata Education, Access, and Care Helpline (REACH), an integrated specialty pharmacy and patient services program, designed to help eligible patients access prescribed Reata medicines. For additional information about REACH programs call 1-844-98-REACH or visit www.reataREACH.com. Reata Pharmaceuticals has partnered with an independent specialty pharmacy specializing in rare disease services to serve as the exclusive SKYCLARYS pharmacy.

Features of Friedreich's ataxia: (Not all inclusive)
Neurological features, such as progressive gait instability, poor balance, impaired coordination, dysarthria, weakness, lower and/or upper limb incoordination, ocular fixation instability, deep sensory loss, and visual and hearing impairment, also diverse non-neurological features such as hypertrophic cardiomyopathy, glucose intolerance or frank diabetes mellitus, kyphoscoliosis (curvature of spine), and foot deformities (high plantar arches – pes cavus).

Modified Friedreich's Ataxia Rating Scale (mFARS): mFARS-Info-Sheet.pdf (curefa.org)

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The mFARS includes assessment and scoring of 4 of the 5 sections of the Friedreich's Ataxia Rating Scale (FARS): bulbar function (scored as 0 to 5), upper limb coordination (scored as 0 to 36), lower limb coordination (scored as 0 to 16), and upright stability (scored as 0 to 36). The mFARS omits the peripheral nervous system evaluation so that all remaining assessments are functional tests. Each section is added together to obtain a total mFARS score. The score ranges from 0 to 93. A lower score indicates better neurological function.

Friedreich ataxia is a slowly progressive disease, and small differences in functional progression over one to two years could translate to meaningful differences over the course of the disease. In a natural history study of individuals with Friedreich ataxia, the mean progression in mFARS scores from baseline was 1.9 points by year 1, 4.2 points by year 2, and 9.6 points by year 5.

Activities of daily living (ADL):

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

Self-care ADL:

Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

Resources:

Skyclarys (omaveloxolone) product information, revised by Biogen. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02255435: A Phase 2 Study of the Safety, Efficacy, and Pharacodynamics of RTA 408 in the treatment of Friedreich's Ataxia (MOXIe). Available from: http://clinicaltrials.gov. Last update posted December 06, 2022. Last verified December 2022. Accessed March 17, 2023. Re-evaluated April 07, 2026.

Lynch DR, Farmer J, Hauser L, et al: Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. Ann Clin Trans 2019; 6(1): 15-25. Accessed March 19, 2023. Re-evaluated April 07, 2026.

Lynch DR, Chin MP, Delatycki MB, et. al: Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). Ann Neurol 2021 Feb; 89 (2): 212-225. Accessed March 19, 2023. Re-evaluated April 07, 2026.

Rummey C, Corben La, Delatycki M, et al.: Natural History of Friedreich Ataxia Heterogenicity of Neurologic Progression and Consequences for Clinical Trial Design. Neurology 2022 Oct;99 (14): e1499-e1510. doi:10.1212/WNL.0000000000200913. Accessed March 19, 2023. Re-evaluated April 07, 2026.

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Reetz K, Dogan I, Costa AS, et al.: Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol 2015 Feb; 14: 174-182. Accessed March 19, 2023. Re-evaluated April 07, 2026.

Rummey C, Corben LA, Delatycki MB, et.al.: Psychometric properties of the Friedreich Ataxia Rating Scale. Neurol Genet 2019;5(6):e371. doi:10.1212/NXG.0000000000000371. Accessed March 20, 2023. Re-evaluated April 07, 2026.