Drug Coverage Policy

Effective Date 8/15/2024
Coverage Policy Number.....IP0566
Policy Title.....Skyclarys

Neurology – Skyclarys

- Skyclarys® (omaveloxolone capsules – Reata/Biogen)

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The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Skyclarys, a nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator, is indicated for the treatment of Friedreich's ataxia in patients ≥ 16 years of age.[1]

Disease Overview
Friedreich's ataxia is an autosomal recessive, progressive, neurodegenerative disorder.[2-6] In the setting of clinical suspicion due to symptoms (e.g., ataxia, cardiomyopathy, scoliosis, and/or diabetes), genetic testing is the cornerstone of confirming a diagnosis of Friedreich's ataxia. A trinucleotide repeat expansion assay to detect biallelic mutations is used.

Clinical Efficacy
In the pivotal study of Skyclarys, patients were 16 to 40 years of age with genetically confirmed Friedreich's ataxia.[1,7] They were required to have a baseline modified Friedreich's Ataxia Rating

Scale (mFARS) between 20 and 80. Patients with pes cavus were allowed to enroll in the study, but their participation was limited to 20% of patients and the primary efficacy analysis did not include patients with pes cavus. Patients with a B-type natriuretic peptide (BNP) > 200 pg/mL or a left ventricular ejection fraction < 40% were also excluded from the study. Uncontrolled diabetes mellitus, defined in a non-pivotal study as a hemoglobin A1c (HbA_{1c}) > 11%, was also part of the exclusion criteria for the pivotal trial.[7,8] The vast majority of patients enrolled in the pivotal trial were ambulatory (93%). The primary efficacy was measured using the mFARS.

Guidelines
Available consensus guidelines on Friedreich's ataxia (2022) identify Skyclarys as a potential investigative agent, but do not make any specific recommendations regarding its use.[6] According to guidelines, patients with Friedreich's ataxia should have an electrocardiogram (EKG) and an echocardiogram at diagnosis and then at least annually. Patients should also be evaluated annually for diabetes mellitus. There is no cure for Friedreich's ataxia; guidelines make extensive recommendations regarding management of the symptoms and complications related to the disease, including diabetes mellitus and cardiomyopathy.

Medical Necessity Criteria

Skyclarys® is considered medically necessary when the following are met:

FDA-Approved Indications

1. **Friedreich's Ataxia.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 16 years of age; AND
     - **ii.** Patient has had genetic testing confirming biallelic pathogenic variants in the frataxin (FXN) gene consistent with a diagnosis of Friedreich's ataxia; AND
     - **iii.** Patient has had ALL of the following in the last year (a, b, and c):
       - **a)** Patient has a B-type natriuretic peptide (BNP) ≤ 200 pg/mL; AND
       - **b)** Patient has a left ventricular ejection fraction ≥ 40%; AND
       - **c)** Patient has a hemoglobin A_{1c} (HbA_{1c}) ≤ 11%; AND
     - **iv.** Patient has been assessed using the modified Friedreich's Ataxia Rating Scale and has a score ≥ 20, but ≤ 80; AND
     - **v.** Patient is ambulatory; AND
     - **vi.** Patient does not have pes cavus; AND
     - **vii.** The medication is prescribed by or in consultation with a neurologist or a physician who specializes in ataxias and/or neuromuscular disorders.
   - **B)** Patient is Currently Receiving Skyclarys. Approve if the patient meets ALL of the following (i, ii, iii, iv and v):
     - **i.** Patient is ≥ 16 years of age; AND
     - **ii.** Patient has had genetic testing confirming biallelic pathogenic variants in the frataxin (FXN) gene consistent with a diagnosis of Friedreich's ataxia; AND
     - **iii.** Patient is ambulatory; AND
     - **iv.** According to the prescriber, the patient continues to benefit from therapy, as demonstrated by a slowed progression on the modified Friedreich's Ataxia Rating Scale; AND
     - **v.** The medication is prescribed by or in consultation with a neurologist, or a physician who specializes in ataxias and/or neuromuscular disorders.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based

literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

1. **Metastatic Melanoma.** Skyclarys has also been evaluated for the treatment of metastatic melanoma (in combination with Opdivo® [nivolumab intravenous infusion] or Yervoy® [ipilimumab intravenous infusion]).[9] Results have not been published. More data are needed.

2. **Mitochondrial Myopathy.** Skyclarys has also been evaluated for the treatment of mitochondrial myopathies. In one Phase II study, following 12 weeks of therapy, no differences in peak workload or 6 minute walk test were observed with Skyclarys vs. placebo.[10] More data are needed to evaluate the efficacy and safety of Skyclarys for mitochondrial myopathy.

References

1. Skyclarys® capsules [prescribing information]. Cambridge, MA: Reata/Biogen; January 2024.
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3. Williams CT, De Jesus OD. Friedreich ataxia. StatPearls [Internet]. Treasure Island, FL. Available at: https://www.ncbi.nlm.nih.gov/books/NBK563199/. Updated August 23, 2023. Accessed on April 22, 2024.
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5. Patel M, Isaacs CJ, Seyer L, et al. Progression of Friedreich ataxia: quantitative characterization of 5 years. *Ann Clin Trans Neurol*. 2016;3(9)684-694.
6. Corben LA, Collins V, Milne S, et al. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. Clinical Management Guidelines Writing Group. *Orphanet J Rare Dis*. 2022;17(1):415. Available at: www.frdaguidelines.org.
7. 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.
8. Lynch DR, Farmer J, Hauser L, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Trans Neurol*. 2018;6(1):15-26.
9. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 Apr 22]. Available from: https://clinicaltrials.gov/. Search term: omaveloxolone.
10. Madsen KL, Buch AE, Cohen BH, et al. Safety and efficacy of omaveloxolone in patients with mitochondrial myopathy: MOTOR trial. *Neurology*. 2020;94(7):e687-e698.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	**Added** 'Patient is Currently Receiving Skyclarys' criteria.	8/15/2024

The policy effective date is in force until updated or retired.