PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Nitisinone Products Prior Authorization Policy
- Harliku™ (nitisinone tablets – Cycle)
- Orfadin® (nitisinone capsules and suspension – Sobi, generic [capsules only])
- Nityr® (nitisinone tablets – Cycle)

REVIEW DATE: 07/16/2025

INSTRUCTIONS FOR USE

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 WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. 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 NATIONAL FORMULARY COVERAGE:

OVERVIEW

Nitisinone products are hydroxy-phenylpyruvate dioxygenase inhibitors. **Orfadin and Nityr** are indicated for the treatment of **hereditary tyrosinemia type 1** in combination with dietary restriction of tyrosine and phenylalanine in adult and pediatric patients.[1,2] **Harliku** is indicated for the treatment of **alkaptonuria** in adults.[3]

Disease Overview

Hereditary Tyrosinemia Type 1

Hereditary tyrosinemia type 1 is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine.[4,5] It is caused by mutations in the *FAH* gene, which lead to a deficiency of the enzyme fumarylacetoacetate hydrolase that is required for

the breakdown of tyrosine. Symptoms usually appear in the first few months after birth and include failure to thrive, diarrhea, vomiting, jaundice, cabbage-like odor, and increased tendency to bleed. Diagnosis is most often via newborn screening (i.e., elevated alpha-fetoprotein and succinylacetone); however, carrier genetic testing and prenatal diagnosis by detection of succinylacetone in the amniotic fluid are also possible. Treatment should be initiated immediately upon diagnosis with a diet restricted in tyrosine and phenylalanine and with nitisinone, which blocks the second step in the tyrosine degradation pathway.

Alkaptonuria

Alkaptonuria is an autosomal recessive genetic disorder, characterized by the accumulation of homogentisic acid in the body.[6,7] It is caused by mutations in the homogentisate 1,2 dioxygenase *(HGD)* gene, which leads to deficiency of the HGD enzyme. This enzyme plays a role in the metabolism of tyrosine and converts homogentisic acid (HGA) into malate and acetoacetate. In the absence of HGD, HGA accumulates in the body. Excess HGA is excreted in the urine, which darkens upon standing due to oxidation. HGA also deposits in connective tissues in a process called ochronosis. Ochronosis results in the blueish-black pigmentation of tissues such as cartilage and sclera. Over time, alkaptonuric ochronosis manifests with progressive musculoskeletal conditions, such as arthritis, ankylosis, and intravertebral disc calcification. Of note, pigmentation changes of the sclera do not affect vision. On exam, the sclera may have brown or gray deposits. Other manifestations due to pigment deposition include stone formation in various organs and valvular heart disease. Diagnosis is generally made by detection of elevated levels of HGA in the urine or molecular genetic testing confirming biallelic pathogenic variants in the *HGD* gene.[7] Treatment with nitisinone in patients maintained on a regular diet has demonstrated an improvement in HGA levels[8-11]; of note, the pivotal study for Harliku utilized Orfadin in its investigation.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nitisinone products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with nitisinone products as well as the monitoring required for adverse events and long-term efficacy, approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Harliku™ (nitisinone tablets – Cycle)**
- **Orfadin® (nitisinone capsules and suspension – Sobi, generic [capsules only])**
- **Nityr® (nitisinone tablets – Cycle)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Hereditary Tyrosinemia Type 1.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the *FAH* gene; OR
     - **ii.** Patient has elevated levels of succinylacetone in the serum or urine; AND
   - **B)** The medication is prescribed in conjunction with a tyrosine- and phenylalanine-restricted diet; AND
   - **C)** Patient will not be taking the requested agent concurrently with another nitisinone product; AND
     Note: Examples of nitisinone products include Orfadin, generic nitisinone capsules, and Nityr. Concurrent use of these agents is not allowed.
   - **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

Other Uses with Supportive Evidence

2. **Alkaptonuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the homogentisate 1,2 dioxygenase (*HGD*) gene; OR
     - **ii.** Patient has elevated levels of homogentisic acid (HGA) in the urine; AND
   - **B)** The medication is prescribed by or in consultation with a rheumatologist or metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

FDA-Approved Indication

1. **Alkaptonuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the homogentisate 1,2 dioxygenase (*HGD*) gene; OR
     - **ii.** Patient has elevated levels of homogentisic acid (HGA) in the urine; AND
   - **B)** The medication is prescribed by or in consultation with a rheumatologist or metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT COVERED

- **Harliku™ (nitisinone tablets – Cycle)**
- **Orfadin® (nitisinone capsules and suspension – Sobi, generic [capsules only])**
- **Nityr® (nitisinone tablets – Cycle)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concomitant Therapy with Nitisinone Products.** Note: For example, concomitant use of Harliku, Orfadin, generic nitisinone capsules, and/or Nityr. There are no data available to support concomitant use.

REFERENCES

1. Orfadin® capsules and suspension [prescribing information]. Waltham, MA: Sobi; November 2021.
2. Nityr® tablets [prescribing information]. Tredegar, UK: PCI Pharma; January 2024.
3. Harliku™ tablets [prescribing information]. Tredegar, UK: PCI Pharma; June 2025.
4. Tyrosinemia type 1. Genetic and Rare Diseases Information Center; National Institutes of Health, US Department of Health and Human Services. Updated September 2024. Available at: https://rarediseases.info.nih.gov/diseases/2658/tyrosinemia-type-1. Accessed on October 31, 2024.
5. Tyrosinemia type 1. National Organization for Rare Disorders. Updated September 2019. Available at: https://rarediseases.org/rare-diseases/tyrosinemia-type-1/. Accessed on October 31, 2024.
6. Alkaptonuria. National Organization for Rare Disorders. Updated June 2017. Available at: https://rarediseases.org/rare-diseases/alkaptonuria/. Accessed on June 17, 202.
7. Introne WJ, Perry M, Chen M. Alkaptonuria. 2003 May 9 [Updated 2021 Jun 10]. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1454/. Accessed on June 17, 2025.
8. Abbas K, Basit J, Rehman MEU. Adequacy of nitisinone for the management of alkaptonuria. *Ann Med Surg (Lond).* 2022;80:104340.
9. Ranganath LR, Milan AM, Hughes AT, et al. Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment. *Ann Rheum Dis.* 2016;75(2):362-7.
10. Ranganath LR, Psarelli EE, Arnoux JB, et al. Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2020;8(9):762-772.
11. Davison AS, Norman BP. Alkaptonuria – Past, present, and future. *Adv Clin Chem.* 2023;114:47-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/15/2023
Annual Revision	No criteria changes.	11/06/2024
Early Annual Revision	Harliku was added to the policy. The criteria was divided based on the specific agent intended for approval. **Orfadin (generics) and Nityr.** Alkaptonuria was added as a condition of approval under "Other Uses with Supportive Evidence". **Harliku.** Alkaptonuria was added as a condition of approval. **Conditions Not Covered**	07/16/2025

	: For concomitant therapy with nitisinone products, Harliku was added to the Note of examples.	