

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)[†] for the treatment of hereditary tyrosinemia, type 1 (HT-1) to be **eligible for coverage**.^{**}

Patient Selection Criteria

Coverage eligibility for nitisinone (Orfadin, Nityr, Harliku, generics) will be considered when the following criteria are met:

- For **Orfadin, Nityr, or generic Orfadin** requests:
 - Patient has a diagnosis of hereditary tyrosinemia, type 1 (HT-1); AND
 - Requested drug will be used in combination with dietary restriction of tyrosine and phenylalanine; AND
 - If the request is for brand Orfadin, there is clinical evidence or patient history that suggests the use of Nityr AND generic nitisinone will be ineffective or cause an adverse reaction to the patient; OR
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - Patient has a diagnosis of alkaptonuria (AKU); AND
 - Patient is greater than or equal to 18 years of age; AND
 - Diagnosis is confirmed by a urinary HGA excretion of greater than 0.4 g/24 hours; AND
 - Patient has clinical manifestations of AKU such as ochronosis or chronic joint pain; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

- If the request is for brand Orfadin, there is clinical evidence or patient history that suggests the use of Nityr AND generic nitisinone will be ineffective or cause an adverse reaction to the patient;
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For **Harliku** requests:
 - Patient has a diagnosis of alkaptonuria (AKU); AND
 - Patient is 18 years of age or older; AND
 - Diagnosis is confirmed by a urinary HGA excretion of greater than 0.4 g/24 hours; AND
 - Patient has clinical manifestations of AKU such as ochronosis or chronic joint pain; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - There is clinical evidence or patient history that suggests the use of Nityr AND generic nitisinone will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand nitisinone (Orfadin) when there is an absence of clinical evidence or patient history that suggests the use of nitisinone (Nityr) AND generic nitisinone (Orfadin) will be ineffective or cause an adverse reaction to the patient to be **not medically necessary.****

Based on review of available data, the Company considers the use of a nitisinone product for AKU when the patient does not have a clinical manifestation of AKU to be **not medically necessary.****

Based on review of available data, the Company considers the use of Harliku for AKU when there is an absence of clinical evidence or patient history that suggests the use of nitisinone (Nityr) AND generic nitisinone (Orfadin) will be ineffective or cause an adverse reaction to the patient to be **not medically necessary.****

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of nitisinone (Orfadin, Nityr, Harliku, generics) when the patient selection criteria are not met (except those noted above as **not medically necessary****) to be **investigational.***

Background/Overview

Nitisinone is an enzyme inhibitor that inhibits 4-hydroxyphenyl-pyruvate dioxygenase and is used in the treatment of two rare metabolic diseases—hereditary tyrosinemia type 1 (HT-1) and alkaptonuria (AKU). It is available in three bioequivalent brands: Orfadin (capsules and suspension), Nityr (tablets), and Harliku (tablets). Orfadin and Nityr are approved by the Food and Drug Administration (FDA) for the treatment of HT-1 and Harliku is approved for the treatment of AKU. However, there are no meaningful differences between Nityr and Harliku except that Nityr is available in multiple tablet strengths (2 mg, 5 mg, 10 mg) and Harliku is only available as a 2 mg tablet. Harliku was approved as a supplemental New Drug Application (sNDA) under Nityr. Orfadin products have a few differentiating qualities. Both the capsules and suspension require refrigeration prior to opening while Nityr and Harliku do not require refrigeration. Additionally, Orfadin capsules must be dosed at least one hour before or two hours after a meal. The Orfadin suspension and Nityr and Harliku tablets do not have a food requirement. Dosing for HT-1 is based on patient weight and serum and urine succinylacetone concentrations. Dosing for AKU is 2 mg once daily. Prior to the availability of Harliku, other nitisinone products were used.

HT-1 is a rare, autosomal recessive disease with a prevalence of 1:12,000 to 1:100,000 individuals of northern European descent. The deficiency in the enzyme fumarylacetoacetate hydrolase and resulting accumulation of toxic metabolites manifests as severe progressive liver disease and renal tubular dysfunction. If untreated, patients have a significantly shortened lifespan often dying of acute liver failure before the second year of life. HT-1 is diagnosed based on the measurement of one of the toxic metabolites, succinylacetone (SA) in either the blood or urine. This test can be performed immediately after birth and is part of routine newborn screening in most states (including Louisiana).

AKU is an ultra-rare inborn error of metabolism characterized by elevated levels of homogentisic acid (HGA) which cause the formation of pigment that is deposited in the bones and cartilage through a process called ochronosis. The hallmark symptom of AKU is urine that darkens when exposed to air or alkalinization. While ochronosis does not typically present until the third decade of life, dark urine may be observable in infants. When ochronosis begins, deposits of brown or blue pigment can be seen in the cartilage of the ear and sclerae, eventually moving to the large joints and spine. As HGA polymers accumulate within the articular cartilage, patients develop ochronotic arthritis/arthropathy, which results in a progressive decline in range of motion. In addition to arthritis, patients also experience pulmonary, cardiac, neurologic, and metabolic complications from ochronosis. Despite substantial morbidity, AKU is not expected to shorten life expectancy. AKU is

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

usually diagnosed based on the detection of elevated HGA in a 24-hour urine collection, but HGA can also be measured via blood or tissue samples. Genetic testing will reveal variations in the homogentisate 1,2 dioxygenase (*HGD*) gene. The treatment of AKU involves addressing individual manifestations as they arise, such as pain management, orthopedic surgery, and physical therapy for arthritis. Although dietary restriction of tyrosine and phenylalanine may theoretically reduce HGA production, and vitamin C inhibits an enzyme involved in the formation of polymers, neither approach has been extensively studied nor shown to significantly improve symptoms or alter the disease course. Nitisinone has been used off-label prior to the approval of Harliku to reduce urine HGA in adults with AKU.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Orfadin and Nityr are indicated for the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Harliku is indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Both Orfadin and Nityr were approved based on an open-label, uncontrolled study of 207 patients with HT-1. All patients were treated with nitisinone in addition to dietary restriction of tyramine and phenylalanine. To assess efficacy, 2 and 4 year survival probabilities were compared to historical controls treated with dietary restriction alone. Patients presenting with HT-1 younger than 2 months of age who were treated with nitisinone and dietary restriction had both 2 and 4 year survival probabilities of 88%. In comparison, historical control patients presenting with HT-1 younger than 2 months of age and treated with dietary restriction alone had both 2 and 4 year survival probabilities of 29%. Patients presenting with HT-1 between ages 2 and 4 months and treated with nitisinone and dietary restriction had both 2 and 4 year survival probabilities of 94%. Historical controls in this group had 2 and 4 year survival probabilities of 74% and 60%, respectively.

This study also evaluated effects on urine and plasma succinylacetone, porphyrin metabolism, and urinary alpha-1-microglobulin and found statistically significant improvements in nitisinone-treated patients compared to pre-treatment baseline.

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

Harliku was approved based on an open-label, single center, randomized, no-treatment controlled trial in 40 adult patients diagnosed with AKU. Patients received either Harliku at 2 mg orally once daily or no treatment for three years. Harliku was effective at reducing levels of urinary HGA. The Harliku group had an average percent reduction from baseline of 88% (95% CI: 79, 97%) after 1 year of treatment, which was sustained through three years of treatment with an average percent reduction from baseline of 91% at year 3 (95% CI: 85, 97%). In contrast, the untreated controls had an average increase of 107% from baseline to year 1 (95% CI: 0, 216%) and 108% from baseline to year 3 (95% CI: 19, 198%).

References

1. Orfadin [package insert]. Apotek. Waltham, MA. Feb 2017.
2. Nityr [package insert]. Rivopharm SA. Manno, Switzerland. September 2020.
3. Harliku [package insert]. Cycle Pharmaceuticals Ltd. Cambridge, CB3 0FA, UK. June 2025.

Policy History

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. New policy.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. No change to coverage.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Added new generic to policy.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Updated Nityr dosing information.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2024	Medical Policy Committee review
11/13/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2025	Medical Policy Committee review
11/12/2025	Medical Policy Implementation Committee approval. Added new product, Harliku, with relevant background information and criteria. Also added criteria for Nityr and Orfadin to allow coverage of alkaptonuria for these products. Title changed from “nitisinone (Orfadin [®] , Nityr [™] , generics)” to “nitisinone (Orfadin [®] , Nityr [™] , Harliku [™] , generics)”.

Next Scheduled Review Date: 11/2026

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

nitisinone (Orfadin[®], Nityr[™], Harliku[™], generics)

Policy # 00586

Original Effective Date: 01/01/2018

Current Effective Date: 12/01/2025

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.