CareSource

PHARMACY POLICY STATEMENT
Nevada Medicaid

DRUG NAME	Nitisinone (Orfadin, Nityr, Harliku)
BENEFIT TYPE	Pharmacy
STATUS	Prior Authorization Required

Nitisinone, approved by the FDA in 2002, is a hydroxy-phenylpyruvate dioxygenase inhibitor indicated for the treatment of adult and pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. It is supplied as generic nitisinone capsules, brand name Orfadin capsules or oral suspension, and brand name Nityr tablets. Nitisinone in combination with prescribed diet leads to far greater survival and clinical outcomes compared to untreated HT-1 patients. Strict adherence to therapy is crucial.

HT-1 is a genetic metabolic disorder that usually presents before 6 months of age. Fumarylacetoacetate hydrolase (FAH) is the deficient enzyme responsible for HT-1. It is the terminal step in the tyrosine catabolic pathway. Mutations in the *FAH* gene lead to HT-1.

Nitisinone inhibits an enzyme in the normal catabolic pathway of tyrosine to prevent accumulation of catabolic intermediates that convert to the toxic metabolites succinylacetone (SA) and succinylacetoacetate (SAA) responsible for the liver and kidney symptoms of HT-1. Neurologic porphyric-like crises may also occur. SA is the primary marker used to screen for HT-1.

In 2025, nitisinone was approved under the brand name Harliku to be indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU). Other nitisinone products have been routinely used off-label for AKU.

Alkaptonuria is a rare genetic metabolic disorder of tyrosine degradation due to deficiency of the third enzyme in the catabolic pathway, caused by mutations in the HGD gene. As a result, homogentisic acid (HGA) accumulates. The three major features of alkaptonuria are dark urine or urine that turns dark on standing (by alkalinization), ochronosis (bluish-black pigmentation in connective tissue), and arthritis of the spine and larger joints.

Nitisinone will be considered for coverage when the following criteria are met:

Hereditary Tyrosinemia Type 1 (HT-1)- Orfadin and Nityr only

For **initial** authorization:

1. Medication must be prescribed by or in consultation with an endocrinologist, geneticist, dietician, hepatologist, or nephrologist; AND
2. Member has a diagnosis of hereditary tyrosinemia type 1 (HT-1) confirmed by at least one of the following:
   a) Biochemical testing (i.e., presence of succinylacetone in the urine or blood)
   b) Genetic test results showing pathogenic mutation of the *FAH* gene; AND
3. Member has a baseline succinylacetone level documented in chart notes; AND
4. Member is using medication in combination with dietary restriction of tyrosine and phenylalanine (commonly found in high-protein food); AND
5. Chart notes must document that the member has had or will have a slit-lamp ophthalmic exam completed prior to initiating treatment; AND

6. If the request is for brand name Orfadin capsules or suspension or Nityr tablets, clinical justification must be provided why generic nitisinone capsules cannot be used.
7. **Dosage allowed/Quantity limit:** Max total daily dosage of 2 mg/kg (orally), based on evaluation of biochemical and/or clinical response. See prescribing info for details.

If all the above requirements are met, the medication will be approved for 12 months.

For **reauthorization**:
1. Member must continue dietary restriction of tyrosine and phenylalanine; AND
2. Chart notes must show a reduced succinylacetone (SA) level compared to baseline.

If all the above requirements are met, the medication will be approved for an additional 12 months.

Alkaptonuria (AKU)- Harliku and generic nitisinone only

For **initial** authorization:
1. Member is at least 18 years of age; AND
2. Medication must be prescribed by or in consultation with a rheumatologist, metabolic specialist, or medical geneticist; AND
3. Member has a documented diagnosis of alkaptonuria confirmed by a significantly elevated amount of HGA in the urine; AND
4. If the request is Harliku, clinical justification must be provided why generic nitisinone capsules cannot be used.
5. **Dosage allowed/Quantity limit:** 2 mg orally once daily. QL: 30 tablets/capsules per 30 days.

If all the above requirements are met, the medication will be approved for 12 months.

For **reauthorization**:
1. Chart notes must show reduced levels of urinary HGA and/or improved symptoms such as joint pain.

If all the above requirements are met, the medication will be approved for an additional 12 months.

CareSource considers nitisinone not medically necessary for the treatment of conditions that are not listed in this document. For any other indication, please refer to the Off-Label policy.

DATE	ACTION/DESCRIPTION
04/30/2020	New policy for Orfadin created.
11/01/2022	Transferred to new template. Renamed policy to generic name and added Nityr brand name. Amended dosing section. Added specialist requirement. Split diagnostic confirmation into 2 parts and added name of mutated gene. Changed wording of slit-lamp exam requirement. Updated references. Added criterion requiring generic caps.
10/11/2024	Annual review; no updates to clinical criteria.
09/19/2025	Added new Harliku product and diagnosis of alkaptonuria.

References:

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2. Nityr [prescribing information]. Cycle Pharmaceuticals Ltd; 2024.
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6. Harliku [prescribing information]. PCI Pharma Services; 2025.
7. Introne WJ, Perry MB, Troendle J, et al. A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. Mol Genet Metab. 2011;103(4):307-314. doi:10.1016/j.ymgme.2011.04.016
8. Introne WJ, Perry M, Chen M. Alkaptonuria. 2003 May 9 [Updated 2021 Jun 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1454/
9. Roopnarinesingh RC, Donlon NE, Reynolds JV. Alkaptonuria: clinical manifestations and an updated approach to treatment of a rare disease. BMJ Case Rep. 2021;14(12):e244240. Published 2021 Dec 7. doi:10.1136/bcr-2021-244240
10. Spears K, et al. O26: Analysis of patient-reported outcomes and a functional assessment from 3-year nitisinone treatment trial in patients with alkaptonuria. Genetics in Medicine Open, Volume 2, Supplement 1, 2024. DOI: 10.1016/j.gimo.2024.100874

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