# Clinical Policy: Nitisinone (Harliku, Nityr, Orfadin)

Reference Number: PA.CP.PHAR.132
Effective Date: 10/20 18
Last Review Date: 10/2025

**Description**
Nitisinone (Harliku™, Nityr™, Orfadin®) is a hydroxy-phenylpyruvate dioxygenase inhibitor.

**FDA Approved Indication(s)**
Nityr and Orfadin are 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.

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

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of PA Health & Wellness® that nitisinone, Harliku, Nityr, Orfadin are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Hereditary Tyrosinemia Type 1** (must meet all)**:**

1. Diagnosis of HT-1 as confirmed by one of the following (a or b);
   a. Genetic testing confirms a mutation of the *FAH* gene;
   b. Biochemical testing confirms elevated levels of succinylacetone in blood or urine;*
   * *The lower limit of normal for succinylacetone is laboratory- and/or treatment center-specific; refer to laboratory- or clinic-specific reference ranges to determine elevated levels.*
2. Request is for generic nitisinone, Nityr, or Orfadin;
3. Prescribed by or in consultation with an endocrinologist or a metabolic or genetic disease specialist;
4. Request is for use as an adjunct to dietary restriction of tyrosine and phenylalanine;
5. Member is not using two different nitisinone products concurrently;
6. For requests for Nityr and Orfadin capsules, member must use generic nitisinone, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed 2 mg/kg per day.

**Approval duration: 12 months**

**B. Alkaptonuria** (must meet all)**:**

1. Diagnosis of AKU;
2. Diagnosis is confirmed by one of the following (a or b):
   a. Baseline urinary HGA excretion greater than 0.4 g/24 hours;

b. HGD (homogentisate 1,2-dioxygenase) biallelic gene mutation (mutations in both copies of the HGD gene) as evidenced by genetic testing;

3. Request is for generic nitisinone or Harliku;
4. Prescribed by or in consultation with an endocrinologist or a metabolic or genetic disease specialist;
5. Age ≥ 18 years;
6. Member is not using two different nitisinone products concurrently;
7. For Harliku requests, member must use generic nitisinone, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose does not exceed 2 mg (one tablet) per day.

**Approval duration: 12 months**

**C. Other diagnoses/indications**

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

## II. Continued Therapy

**A. Hereditary Tyrosinemia Type 1** (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. Request is for use as an adjunct to dietary restriction of tyrosine and phenylalanine;
4. Member is not using two different nitisinone products concurrently;
5. For requests for Nityr and Orfadin capsules, member must use generic nitisinone, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for a dose increase, new dose does not exceed 2 mg/kg per day.

**Approval duration: 12 months**

**B. Alkaptonuria** (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Reduced levels of urinary HGA;
   b. Improved joint (e.g., hip, spine, knee, shoulder) symptoms (e.g., range of motion, pain, stiffness);
3. Member is not using two different nitisinone products concurrently;
4. For Harliku requests, member must use generic nitisinone, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 2 mg (one tablet) per day.

**Approval duration: 12 months**

**C. Other diagnoses/indications** (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

AKU: alkaptonuria
FDA: Food and Drug Administration
HGA: urine homogentisic acid
HGD: homogentisate 1,2-dioxygenase
HT-1: hereditary tyrosinemia type 1

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| nitisinone (Orfadin) | HT-1<br>0.5 mg/kg PO BID<br><br>AKU<br>2mg PO QD | HT-1<br>2 mg/kg<br><br>AKU<br>2 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

None reported

## V. Dosage and Administration

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| Nitisinone (Harliku) | AKU | 2 mg PO QD | 2 mg/day |
| Nitisinone (Nityr, Orfadin) | HT-1 | 0.5 mg/kg PO BID | 2 mg/kg |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Nitisinone (Nityr) | Tablets: 2 mg, 5 mg, 10 mg |
| Nitisinone (Harliku) | Tablets: 2 mg |
| Nitisinone (Orfadin) | Capsules: 2 mg, 5 mg, 10 mg, 20 mg |

| Drug Name | Availability |
|---|---|
| | Oral suspension: 4 mg/mL |

## VII. References

1. Harliku Prescribing Information. Cambridge, United Kingdom: Cycle Pharmaceuticals Ltd; June 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209449s018lbl.pdf. Accessed July 15, 2025.
2. Orfadin Prescribing Information. Waltham, MA: Sobi, Inc.; November 2021. Available at: http://www.orfadin.com/. Accessed July 15, 2025.
3. Nityr Prescribing Information. Centro Insema, Manno Switzerland: Rivopharm; January 2024. Available at: www.nityr.us. Accessed July 15, 2025.
4. Chinsky JM, Singh R, Ficicioglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genetics in Medicine. Dec 2017;19(12).
5. Van Ginkel WG, Rodenburg IL, Harding CO, et al. Long-term outcomes and practical considerations in the pharmacological management of tyrosinemia type 1. Pediatr Drugs. 2019;21:413–26. https://doi.org/10.1007/s40272-019-00364-4.
6. Spears KR, Rossignol F, Perry MB, et al. Patient-reported outcomes and functional assessments of patients with Alkaptonuria in a 3-year Nitisinone treatment trial. Mol Genet Metab. 2024 Sep-Oct; 143(1-2): 108562.
7. Long-term study of nitisinone to treat alkaptonuria. August 26, 2021. ClinicalTrials.gov Identifier: NCT 00107783. Available at: https://clinicaltrials.gov/study/NCT00107783. Accessed June 23, 2025.

| Reviews, Revisions, and Approvals | Date |
|---|---|
| Policy created | 10/2018 |
| 4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020 | 10/2019 |
| 4Q 2020 annual review: added requirement for adjunctive dietary restriction of tyrosine and phenylalanine, in line with the FDA-approved indication; references reviewed and updated. | 10/2020 |
| 4Q 2021 annual review: added requirement for diagnosis confirmation by either genetic or biochemical testing; references reviewed and updated. | 10/2021 |
| 4Q 2022 annual review: no significant changes; references reviewed and updated. | 10/2022 |
| 4Q 2023 annual review: no significant changes; added exclusion against concomitant use of multiple different nitisinone products; added generic redirection for 2 mg, 5 mg, 10 mg strengths (generic nitisinone 20 mg strength is either NF or same tier level as brand Orfadin 20 mg); references reviewed and updated. | 10/2023 |
| 4Q 2024 annual review: Per SDC, for Orfadin revised generic redirection to apply generally to the capsule formulation (to now include the 20 mg strength); references reviewed and updated. | 10/2024 |

| Reviews, Revisions, and Approvals | Date |
|---|---|
| 4Q 2025 annual review: RT4: added Harliku to criteria along with new criteria set for alkaptonuria; extended initial approval durations to 12 months; references reviewed and updated | 10/2025 |