Clinical Policy: Nitisinone (Harliku, Nityr, Orfadin)

Reference Number: CP.PHAR.132
Effective Date: 08.28.18
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® that Harliku, Nityr, Orfadin, and generic nitisinone 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 capsule, 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: 6 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: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving generic nitisinone, Nityr, or Orfadin via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
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 capsule, 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. Member meets one of the following (a or b):
   a. Currently receiving generic nitisinone or Harliku via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HGD: homogentisate 1,2-dioxygenase
HT-1: hereditary tyrosinemia type 1
HGA: urine homogentisic acid
AKU: alkaptonuria

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
generic nitisinone (Orfadin)	HT-1 0.5 mg/kg PO BID AKU 2 mg PO QD	HT-1 2 mg/kg AKU 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 (Harliku)	Tablets: 2 mg
Nitisinone (Nityr)	Tablets: 2 mg, 5 mg, 10 mg
Nitisinone (Orfadin)	Capsules: 2 mg, 5 mg, 10 mg, 20 mg 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 June 23, 2025.
2. Orfadin Prescribing Information. Waltham, MA: Sobi, Inc.; November 2021. Available at: http://www.orfadin.com/. Accessed July 15, 2024.
3. Nityr Prescribing Information. Manno, Switzerland: Rivopharm; January 2024. Available at: www.nityr.us. Accessed August 8, 2024.

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	P&T Approval Date
4Q 2020 annual review: added requirement for adjunctive dietary restriction of tyrosine and phenylalanine, in line with the FDA-approved indication; removed references to HIM non-formulary policy for Nityr; references reviewed and updated.	08.03.20	11.20
4Q 2021 annual review: added requirement for diagnosis confirmation by either genetic or biochemical testing; revised HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	08.17.21	11.21
4Q 2022 annual review: no significant changes; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.27.22	11.22
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.	08.11.23	11.23
Per March SDC, for Orfadin revised generic redirection to apply generally to the capsule formulation (to now include the 20 mg strength).	03.12.24	05.24
4Q 2024 annual review: no significant changes; references reviewed and updated.	07.15.24	11.24
RT4: added Harliku to criteria along with new criteria set for alkaptonuria.	06.23.25	08.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical

policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.