Original Effective Date: 07/01/2018
Current Effective Date: 10/12/2025
Last P&T Approval/Version: 07/30/2025
Next Review Due By: 07/2026
Policy Number: C13398-A

Nitisinone (Harliku, Orfadin, Nityr)

PRODUCTS AFFECTED

Harliku (nitisinone), Nityr (nitisinone), nitisinone, Orfadin (nitisinone)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hereditary tyrosinemia type 1, Alkaptonuria

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. HEREDITARY TYROSINEMIA TYPE 1 (NITYR, ORFADIN ONLY):
1. Documented diagnosis of hereditary tyrosinemia type 1 (HT-1)
   AND

2. Documentation diagnosis was confirmed by detection of elevated succinyl acetone (SA) in blood or urine OR DNA testing confirming mutation in the fumarylacetoacetate hydrolase (FAH) gene [DOCUMENTATION REQUIRED]
   AND
3. Documentation of baseline succinyl acetone (SA) level [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attestation member has been counseled regarding dietary restriction of tyrosine and phenylalanine
   AND
5. Prescriber attests baseline ophthalmologic testing, hepatic imaging and baseline labs have been obtained and reviewed such as: liver evaluation (PT, PTT, ALT/AST), renal function (BUN, creatine, etc.), plasma amino acids, and a complete blood count (CBC), and serum alpha- fetoprotein (AFP)
   AND
6. FOR ORFADIN REQUESTS: Clinical evidence or medical record documenting the use of Nityr will be ineffective or cause an adverse reaction to the member

B. ALKAPTONURIA (HARLIKU ONLY):
1. Documented diagnosis of alkaptonuria
   AND
2. Documentation diagnosis was confirmed by urinary homogentisic acid (HGA) and genetic defect of the *HGD* gene
   AND
3. Documentation of baseline urinary homogentisic acid (HGA)

CONTINUATION OF THERAPY:

A. HEREDITARY TYROSINEMIA TYPE 1 (NITYR, ORFADIN ONLY):
1. Prescriber attestation that there has been monitoring for plasma amino acids, liver function, serum AFP increases, CBC, and ophthalmologic side effects testing
   Note: Patients with hereditary tyrosinemia type I are at increased risk of developing porphyric crises, hepatic neoplasms, and liver failure requiring liver transplantation. Regular monitoring of the liver by imaging and laboratory tests, including serum alpha-fetoprotein concentrations, is recommended. An increase in alpha-fetoprotein concentrations may be a sign of inadequate nitisinone treatment, but patients with increasing alpha-fetoprotein concentrations or signs of nodules in the liver during treatment with nitisinone should always be evaluated for hepatic malignancy.
   AND
2. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
3. Documentation urinary or blood succinyl acetone (SA) levels have decreased from baseline while on treatment with nitisinone [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests to or clinical review has found no evidence of intolerable adverse effects or drug toxicity (e.g., corneal ulcers, corneal opacities, keratitis, conjunctivitis, ocular pain, photophobia, etc.)

C. ALKAPTONURIA (HARLIKU ONLY):
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (i.e., elevated tyrosine levels, corneal ulcers, corneal opacities, keratitis,

conjunctivitis, ocular pain, photophobia, etc.)
AND

3. Documentation urinary homogentisic acid (HGA) levels have decreased from baseline while on treatment with nitisinone [DOCUMENTATION REQUIRED]

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a specialist in metabolic or genetic disease, or in the treatment of hereditary tyrosinemia type 1 (HT-1) or alkaptonuria (AKU) [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
Nityr, Orfadin: No restriction
Harliku: 18 years of age and older

QUANTITY:
HT-1: Maximum 1 mg/kg orally twice daily (2 mg/kg/day)
AKU: 2mg daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Hereditary Tyrosinemia Type 1 (HT-1) Treatment - Agents

FDA-APPROVED USES:
Indicated for the treatment of adult and pediatric patients with hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine. Indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Hereditary Tyrosinemia Type 1 (HT-1): a rare metabolic disease in children. In normal, unaffected individuals, excess amounts of the amino acid tyrosine are degraded in several steps. In HT-1, however, one of the enzymes in this degradation, fumarylacetoacetase hydrolase (FAH), is deficient. Tyrosine and its toxic metabolites [fumarylacetoacetate, maleylacetoacetate, succinyl acetone (SA), and succinyl acetoacetate (SAA)] thus build up in the body and cause serious medical problems such as liver failure and hepatocellular carcinoma. Kidney dysfunction, skeletal changes, and neurological manifestations may also occur.
Orfadin and Nityr are both indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination

with dietary restriction of tyrosine and phenylalanine. HT-1 is the most severe disorder of tyrosine metabolism. Fumarylacetoacetate (FAA) causes damage as it accumulates in the liver and kidney. FAA also causes oxidative damage to cells. To diagnose a patient with HT-1 the metabolites ofFAA, succinyl acetoacetate (SAA) and succinyl acetone (SA), can be measured.
Nitisinone is the primary treatment for HT-1 as it limits formation of the toxic compounds such as FAA and its metabolite SA.

Alkaptonuria is a rare, autosomal recessive genetic disorder that results from deficient activity of homogentisic acid dioxygenase (HGD), the third enzyme in tyrosine degradation. HGD deficiency results in elevated levels of homogentisic acid (HGA), which polymerizes, forming a pigment that is deposited in connective tissue throughout the body (ochronosis). Additionally, buildup of HGA can result in osteoarthritis and complications in the heart and kidneys. Patients often develop pain and reduced joint mobility, requiring large joint replacements.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Nitisinone (Harliku, Orfadin, Nityr) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Nitisinone include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Nityr TABS 2MG, 5MG & 10MG
Nitisinone CAPS 2MG, 5MG, 10MG, & 20MG
Orfadin CAPS 2MG, 5MG, 10MG, & 20MG
Orfadin SUSP 4MG/ML

REFERENCES

1. Nityr (nitisinone) tablets, for oral use [prescribing information]. Cambridge, UK: Cycle Pharmaceuticals Ltd; May 2024.
2. Orfadin (nitisinone) capsules, for oral use; oral suspension [prescribing information]. Waltham, MA: Sobi, Inc.; November 2021.
3. Harliku (nitisinone) tablets, for oral use [prescribing information]. Cambridge, UK: Cycle Pharmaceuticals Ltd; June 2025.
4. Chinsky, JM et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group

review and recommendations. Genet Med. 2017 Dec; 19(12). doi: [10.1038/gim.2017.101]

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Updated Name Products Affected Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Age Restrictions Quantity FDA-Approved Uses Background References	Q3 2025
REVISION- Notable revisions: Required Medical Information References	Q3 2024
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy FDA-Approved Uses Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Contraindications/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file