09-J1000-27

Original Effective Date: 07/15/10

Reviewed: 10/08/25

Revised: 01/01/26

Subject: Nitisinone (Orfadin®, Nityr™, Harliku™)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Nitisinone (Orfadin®, Nityr™, Harliku™) is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in persons with **hereditary tyrosinemia type 1** (HT-1), nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In persons with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1.

Since nitisinone inhibits catabolism of tyrosine, use of this drug can result in elevated plasma levels of this amino acid. Treatment with nitisinone, therefore, requires restriction of the daily intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine.

The safety and efficacy of nitisinone for the treatment of alkaptonuria (AKU) was evaluated in a single-center, open-label, randomized, no-treatment controlled trial in adults with AKU (n=40; NCT00107783). Patients were enrolled in the trial if they were between 30 and 80 years of age, had an established diagnosis of AKU based on urinary HGA excretion of >0.4 g/24 hour, and had evidence of hip involvement (pain or decreased range of motion) but at least one hip joint remaining (bilateral hip replacement patients were excluded). Patients received either nitisinone 2 mg orally once daily or no treatment for a duration of 3 years.

After 1 year of treatment with nitisinone, the primary endpoint of urinary HGA levels were reduced from baseline by an average of 88% (95% CI, 79% to 97%); this was maintained through year 3 of treatment

with an average reduction from baseline of 91% (95% CI, 85% to 97%). Untreated control patients had an average increase from baseline of 107% (95% CI, 0% to 216%) at year 1 and 108% (95% CI, 19% to 198%) at year 3.

Common adverse reactions observed in the nitisinone group included elevated tyrosine levels (95%), keratitis (15%), and thrombocytopenia (10%). One patient in the nitisinone group died after experiencing atrial fibrillation and had discontinued treatment one month prior to death, and 2 patients in the no-treatment control group discontinued the study early.

Nitisinone for AKU was originally submitted as a supplemental New Drug Application (sNDA) under brand Nityr, However, Harliku received its own brand name by the FDA upon approval. There are no meaningful differences in the products except that Nityr is available in higher strengths, which are not required for AKU. Despite this, the annual cost of Harliku exceeds other nitisinone products by more than $500,000.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation and continuation of nitisinone (Orfadin, Nityr, Harliku) **meets the definition of medical necessity** for the following indications when **ALL** of the indication-specific criteria are met:

1. Hereditary Tyrosinemia Type 1 (HT-1)
    a. Member is diagnosed with HT-1 – documentation from the medical record must be provided
    b. Nitisinone will be used as an adjunct to dietary restriction of tyrosine and phenylalanine
    c. Member meets one of the following
        i. Requested product is generic nitisinone
        ii. Requested product is brand Orfadin **AND** the member has tried and had intolerable adverse effects to generic nitisinone – **ALL** of the following must be submitted
            1. The specific intolerance(s) and rationale for using brand Orfadin must be specified
            2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/formsreporting-fda
            3. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjoalgorithm.pdf

iii. Requested product is brand Nityr **AND** the member has tried and had intolerable adverse effects to generic nitisinone – **ALL** of the following must be submitted:

1. The specific intolerance(s) and rationale for using brand Nityr must be specified
2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/formsreporting-fda
3. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjoalgorithm.pdf

2. Alkaptonuria (AKU)
   a. Member is diagnosed with AKU – documentation from the medical record must be provided
   b. Member's urinary homogentistic acid (HGA) excretion is greater than or equal to 1 gram/24 hours – laboratory documentation must be provided
   c. Member has ochronosis of connective tissues (e.g., bluish-black pigmentation of the eyes, ears, or nose) – documentation from the medical record must be provided
   d. Member has arthritis in the spine and large joints (e.g., hip, knee, shoulder)
   e. Member meets one of the following:
      i. Requested product is generic nitisinone
      ii. Requested product is brand Orfadin **AND** the member has tried and had intolerable adverse effects to generic nitisinone – **ALL** of the following must be submitted:
         1. The specific intolerance(s) and rationale for using brand Orfadin must be specified
         2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/formsreporting-fda
         3. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjoalgorithm.pdf
      iii. Requested product is brand Nityr **AND** the member has tried and had intolerable adverse effects to generic nitisinone – **ALL** of the following must be submitted:
         1. The specific intolerance(s) and rationale for using brand Nityr must be specified
         2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/formsreporting-fda
         3. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjoalgorithm.pdf
      iv. Requested product is brand Harliku **AND** all other nitisinone products (generic nitisinone, Orfadin, Nityr) are unavailable for use due to a national drug shortage* - documentation of the shortage must be provided

*To verify non-availability, the status of generic nitisinone capsules, brand Orfadin capsules, brand Orfadin oral solution, **AND** brand Nityr tablets must be listed as "Currently in Shortage" on the FDA Drug Shortages webpage (http://www.accessdata.fda.gov/scripts/drugshortages/) **AND** all listed manufactures must have **ALL** strengths unavailable.

f. Dose does not exceed 2 mg daily

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

- HT-1 The recommended initial dosage is 0.5 mg/kg orally twice daily
- AKU: The recommended dosage of HARLIKU is 2 mg administered orally, once daily

Dosage adjustment:

- HT-1
  - Titrate the dose based on biochemical and/or clinical response, as described in the full prescribing information
  - The maximum dosage is 1 mg/kg orally twice daily
  - If the biochemical parameters (except plasma succinylacetone) are not normalized within 1 month after start of treatment, the dosage should be increased to 1.5 mg/kg/day. For plasma succinylacetone, it may take up to 3 months before the level is normalized after the start of treatment. A dosage of 2 mg/kg/day may be needed once liver function has improved.

Drug Availability:

- Capsules (generic nitisinone, Orfadin): 2 mg, 5 mg, 10 mg, 20 mg
- Oral suspension (Orfadin): 4 mg/mL
- Tablets (Nityr): 2 mg, 5 mg, 10 mg
- Tablets (Harliku): 2 mg

PRECAUTIONS:

High plasma tyrosine levels: Inadequate restriction of tyrosine and phenylalanine intake can result in elevations in plasma tyrosine. Plasma tyrosine levels should be kept below 500 mcmol/L in order to avoid toxic effects to the eyes (corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia), skin (painful hyperkeratotic plaques on the soles and palms), and nervous system (variable degrees of mental retardation and developmental delay).

Transient thrombocytopenia and leucopenia: Subjects treated with nitisinone and dietary restriction in clinical trials were observed to develop transient thrombocytopenia (3%), leucopenia (3%), or both

(1.5%). Monitor platelet and white blood cell counts regularly in persons administered nitisinone therapy.

Monitoring: It is appropriate during regular monitoring to follow urine succinylacetone, ver function tests, alpha-fetoprotein, platelets, white blood cell counts, and serum tyrosine and phenylalanine levels. However, during the initiation of therapy and during acute exacerbations, it may be necessary to follow more closely all available biochemical parameters (e.g., plasma nitisinone concentration, plasma succinylacetone levels, urine 5-ALA levels, and erythrocyte PBG-S activity). Regular liver monitoring by imaging (ultrasound, computerized tomography, magnetic resonance imaging) is recommended. Measure serum phosphate as a screening test for individuals with renal involvement at risk for secondary hypophosphatemia and rickets. Perform slit-lamp examinations of the eyes before initiation of treatment and during any eye adverse reactions (e.g., photophobia, eye pain, signs of inflammation).

BILLING/CODING INFORMATION:

Oral agents are generally administered through the pharmacy benefit.

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic

ICD-10 Diagnosis Codes That Support Medical Necessity

E70.21	Tyrosinemia
E70.29	Alkaptonuria

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Alkaptonuria: a rare inherited genetic disorder of phenylalanine and tyrosine metabolism. It is an autosomal recessive condition that is due to a defect in the enzyme homogentisate 1,2-dioxygenase, which participates in the degradation of tyrosine. As a result, homogentisic acid and its oxide, called alkapton, accumulate in the blood and are excreted in urine in large amounts. Excessive homogentisic acid causes damage to cartilage and heart valves as well as precipitating as kidney stones.

Hereditary tyrosinemia type 1: A metabolic disorder in which an enzyme critical for the breakdown of the amino acid tyrosine is missing. This allows abnormal amounts of tyrosine to accumulate in the body and act like as a poison causing damage, especially in the liver.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

REFERENCES:

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5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 9/20/25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
6. Swedish Orphan Biovirum AB. Orfadin (nitisinone) capsule. 2017 [cited 9/20/17]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d449b73-d503-4132-b978-d890491975df/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/08/25.

GUIDELINE UPDATE INFORMATION:

07/15/10	New Medical Coverage Guideline.

06/15/11	Review and revision to guideline; consisting of updating references.
06/15/12	Review and revision to guideline; consisting of updating coding and references.
06/15/13	Review and revision to guideline; consisting of revising position statement to include orphan drug indication and approval duration, revising dosage/administration and precautions section, adding pertinent definitions, and updating references and program exceptions. No longer reviewed.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/17	Revision to guideline to include Nityr in position statement, dosing and administration, references.
01/01/26	Review and revision to guideline to include Harliku in position statement, dosing and administration, references