VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Nitisinone Products Prior Authorization Policy
- Harliku™ (nitisinone tablets – Cycle)
- Orfadin® (nitisinone capsules and suspension – Sobi, generic [capsules only])
- Nityr® (nitisinone tablets – Cycle)

REVIEW DATE: 07/16/2025

OVERVIEW

Nitisinone products are hydroxy-phenylpyruvate dioxygenase inhibitors. **Orfadin and Nityr** are indicated for the treatment of **hereditary tyrosinemia type 1** in combination with dietary restriction of tyrosine and phenylalanine in adult and pediatric patients.[1,2] **Harliku** is indicated for the treatment of **alkaptonuria** in adults.[3]

Disease Overview

Hereditary Tyrosinemia Type 1

Hereditary tyrosinemia type 1 is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine.[4,5] It is caused by mutations in the *FAH* gene, which lead to a deficiency of the enzyme fumarylacetoacetate hydrolase that is required for the breakdown of tyrosine. Symptoms usually appear in the first few months after birth and include failure to thrive, diarrhea, vomiting, jaundice, cabbage-like odor, and increased tendency to bleed. Diagnosis is most often via newborn screening (i.e., elevated alpha-fetoprotein and succinylacetone); however, carrier genetic testing and prenatal diagnosis by detection of succinylacetone in the amniotic fluid are also possible. Treatment should be initiated immediately upon diagnosis with a diet restricted in tyrosine and phenylalanine and with nitisinone, which blocks the second step in the tyrosine degradation pathway.

Alkaptonuria

Alkaptonuria is an autosomal recessive genetic disorder, characterized by the accumulation of homogentisic acid in the body.[6,7] It is caused by mutations in the homogentisate 1,2 dioxygenase *(HGD)* gene, which leads to deficiency of the HGD enzyme. This enzyme plays a role in the metabolism of tyrosine and converts homogentisic acid (HGA) into malate and acetoacetate. In the absence of HGD, HGA accumulates in the body. Excess HGA is excreted in the urine, which darkens upon standing due to oxidation. HGA also deposits in connective tissues in a process called ochronosis. Ochronosis results in the blueish-black pigmentation of tissues such as cartilage and sclera. Over time, alkaptonuric ochronosis manifests with progressive musculoskeletal conditions, such as arthritis, ankylosis, and intravertebral disc calcification. Of note, pigmentation changes of the sclera do not affect vision. On exam, the sclera may have brown or gray deposits. Other manifestations due to pigment deposition include stone formation in various organs and valvular heart disease. Diagnosis is generally made by detection of elevated levels of HGA in the urine or molecular genetic testing confirming biallelic pathogenic variants in the *HGD* gene.[7] Treatment with nitisinone in patients maintained on a regular diet has demonstrated an improvement in HGA levels[8-11]; of note, the pivotal study for Harliku utilized Orfadin in its investigation.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nitisinone products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with nitisinone products as well as the monitoring required for adverse events

and long-term efficacy, approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of nitisinone products is recommended in those who meet the following criteria:

FDA-Approved Indication

I. Coverage of **Orfadin (generics) and Nityr** is recommended in those who meet one of the following criteria:

1. **Hereditary Tyrosinemia Type 1.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the *FAH* gene; OR
     - **ii.** Patient has elevated levels of succinylacetone in the serum or urine; AND
   - **B)** The medication is prescribed in conjunction with a tyrosine- and phenylalanine-restricted diet; AND
   - **C)** Patient will not be taking the requested agent concurrently with another nitisinone product; AND
     Note: Examples of nitisinone products include Orfadin, generic nitisinone capsules, and Nityr. Concurrent use of these agents is not allowed.
   - **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

Other Uses with Supportive Evidence

2. **Alkaptonuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the homogentisate 1,2 dioxygenase (*HGD*) gene; OR
     - **ii.** Patient has elevated levels of homogentisic acid (HGA) in the urine; AND
   - **B)** The medication is prescribed by or in consultation with a rheumatologist or metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

II. Coverage of **Harliku** is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Alkaptonuria.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** According to the prescriber, diagnosis is supported by ONE of the following (i or ii):
     - **i.** Genetic testing confirms biallelic pathogenic or likely pathogenic variants in the homogentisate 1,2 dioxygenase (*HGD*) gene; OR
     - **ii.** Patient has elevated levels of homogentisic acid (HGA) in the urine; AND
   - **B)** The medication is prescribed by or in consultation with a rheumatologist or metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of nitisinone products is not recommended in the following situations:

1. **Concomitant Therapy with Nitisinone Products.** Note: For example, concomitant use of Harliku, Orfadin, generic nitisinone capsules, and/or Nityr. There are no data available to support concomitant use.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/15/2023
Annual Revision	No criteria changes.	11/06/2024
Early Annual Revision	Harliku was added to the policy. The criteria was divided based on the specific agent intended for approval. **Orfadin (generics) and Nityr.** Alkaptonuria was added as a condition of approval under "Other Uses with Supportive Evidence". **Harliku.** Alkaptonuria was added as a condition of approval. **Conditions Not Recommended for Approval:** For concomitant therapy with nitisinone products, Harliku was added to the Note of examples.	07/16/2025