BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

HARLIKU™ (nitisinone (aku)) tablet
Nitisinone capsule
NITYR™ (nitisinone) tablet
ORFADIN® (nitisinone) capsule and suspension
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for HARLIKU (nitisinone)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Pediatrician or Geneticist or in consultation with a Pediatrician or Geneticist

Indication
- Alkaptonuria (for reduction of urine homogentisic acid)

ORIGINAL EFFECTIVE DATE: 07/21/2016 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/21/2025

- Hereditary tyrosinemia type 1

Age Requirement

- 30 years of age or older for alkaptonuria

Baseline Clinical Evaluation

- **For hereditary tyrosinemia type 1:** Diagnosis supported by **ONE** of the following:
  - Genetic test confirming biallelic pathogenic or likely pathogenic variants in the FAH gene
  - Plasma or urine succinylacetone (SA) are elevated prior to treatment
- **For alkaptonuria:** Diagnosis supported by **ONE** of the following:
  - Deficient activity of homogentisic acid dioxygenase (HGD) enzyme
  - Mutation in homogentisate 1,2 dioxygenase (HGO) gene **ALL** of the following:
- Ophthalmologic examination including slit lamp examination
- Plasma tyrosine level
- Elevated homogentisic acid (HGA) level in blood and urine
- Urinary HGA greater than 0.4 g/24h
- Clinical features such as:
  - Dark or black urine if left standing
  - Pigmented ear cartilage and sclerae
  - Pigmentation in large joints and spine (especially lumbosacral)
  - Radiographic evidence of calcifications of multiple intervertebral discs
  - Ochronotic arthritis with progressive limitations in motion
  - Arthropathy of either hip, knee, or shoulder
  - Axillary and inguinal areas with a brownish discoloration

Alternative Therapies

- Failure after adequate trial, contraindication per FDA label, or intolerance to generic nitisinone capsule

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Additional Requirements

- No concomitant use with nitisinone capsule or suspension
- Will be used in combination with dietary restriction of tyrosine and phenylalanine

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Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (e.g., homogentisic acid levels, urinary homogentisic acid excretion, homogentisic acid dioxygenase (HGD) enzyme, plasma tyrosine, plasma or urine succinylacetone (SA), genetic testing
  - Supporting clinical documentation (ophthalmologic examination)

Initial Therapy Criteria Approval Duration:
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification
- Continues to be seen by a Pediatrician or Geneticist or is in consultation with a Pediatrician or Geneticist

Clinical Response
- **For hereditary tyrosinemia type 1: BOTH** of the following:
  - **ALL** of the following:
    1. Achieved and maintains a plasma tyrosine level below 500 micromol/L through dietary restriction of tyrosine and phenylalanine intake
    2. Urinary succinylacetone (SA) level is less than 1 mmol/mol creatinine
    3. Plasma SA level is less than 0.1 micromol/L
  - **TWO** of the following:
    1. Alpha fetoprotein (AFP) level has decreased
    2. Urinary alpha 1 microglobulin has decreased
    3. Urine 5 amino levulinate (ALA) has decreased
- **For Alkaptonuria: TWO** of the following :
  - Reduction of urinary homogentisic acid (HGA)
  - Reduction of serum homogentisic acid (HGA)
  - Improvement in signs and symptoms of alkaptonuria

Adherence
- Adherence to the prescribed therapy regimen and dietary restriction of tyrosine and phenylalanine has been documented

Alternative Therapies
- Failure after adequate trial, contraindication per FDA label, or intolerance to generic nitisinone capsule

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Generic Equivalent (if available)

Brand Specific Criteria
- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No significant adverse drug effects such as:
  - Conjunctivitis, corneal ulcers, corneal opacities, eye pain, keratitis, photophobia, redness, swelling, and burning of the eyes
  - Painful hyperkeratotic plaques on the soles and palms
  - Liver failure
  - Porphyria
  - Leukopenia
  - Severe thrombocytopenia
- Nitisinone tablets will not be used simultaneously with nitisinone capsule or suspension

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration:
- 12 months OR end of plan year

Medical Necessity Requirements for NITISINONE capsule generic, NITYR (nitisinone), and ORFADIN (nitisinone)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Pediatrician or Geneticist or in consultation with a Pediatrician or Geneticist

Indication
- Hereditary tyrosinemia type 1 (hepatorenal tyrosinemia)
- Alkaptonuria

PHARMACY COVERAGE GUIDELINE

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Generic Equivalent (if available)

Baseline Clinical Evaluation

- **For hereditary tyrosinemia type 1:** Diagnosis supported by **ONE** of the following:
  - Genetic test confirming biallelic pathogenic or likely pathogenic variants in the FAH gene
  - Plasma or urine succinylacetone (SA) are elevated prior to treatment
- **For alkaptonuria:** Diagnosis supported by **ONE** of the following:
  - Deficient activity of homogentisic acid dioxygenase (HGD) enzyme
  - Mutation in homogentisate 1,2 dioxygenase (HGO) gene **ALL** of the following:
- Ophthalmologic examination including slit lamp examination
- Plasma tyrosine level
- Serum and urine alpha fetoprotein
- Urine 5 aminolevulinic acid
- Erythrocyte porphobilinogen synthase activity

Alternative Therapies

- Failure after adequate trial, contraindication per FDA label, or intolerance to generic nitisinone capsule

Brand Specific Criteria

- **For Nityr (nitisinone):** Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (see Definitions section)

Additional Requirements

- **For Orfadin suspension:** documented inability to swallow oral solid dosage forms due to **ANY** of the following:
  - Individual is less than 5 years of age
  - Severe dysphagia
  - Esophagitis with strictures or narrowing
  - Has a feeding tube
  - Radiation therapy to head and neck for cancer
- No concomitant use with nitisinone capsule or suspension
- Will be used in combination with dietary restriction of tyrosine and phenylalanine

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (e.g., homogentisic acid levels, urinary homogentisic acid excretion, homogentisic acid dioxygenase (HGD) enzyme, plasma and urine succinylacetone, plasma tyrosine level, Serum and urine alpha fetoprotein, urine 5 aminolevulinic acid, erythrocyte porphobilinogen synthase activity

- Supporting clinical documentation (e.g., ophthalmologic exam)

Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a Pediatrician or Geneticist or is in consultation with a Pediatrician or Geneticist

Clinical Response

- **For hereditary tyrosinemia type 1: BOTH** of the following:
  - **ALL** of the following:
    4. Achieved and maintains a plasma tyrosine level below 500 micromol/L through dietary restriction of tyrosine and phenylalanine intake
    5. Urinary succinylacetone (SA) level is less than 1 mmol/mol creatinine
    6. Plasma SA level is less than 0.1 micromol/L
  - **TWO** of the following:
    4. Alpha fetoprotein (AFP) level has decreased
    5. Urinary alpha 1 microglobulin has decreased
    6. Urine 5 amino levulinate (ALA) has decreased
- **For Alkaptonuria: TWO** of the following :
  - Reduction of urinary homogentisic acid (HGA)
  - Reduction of serum homogentisic acid (HGA)
  - Improvement in signs and symptoms of alkaptonuria

Adherence

- Adherence to the prescribed therapy regimen and dietary restriction of tyrosine and phenylalanine has been documented

Alternative Therapies

- Failure after adequate trial, contraindication per FDA label, or intolerance to generic nitisinone capsule

Brand Specific Criteria

- **For Nityr and Orfadin capsule:** Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

PHARMACY COVERAGE GUIDELINE

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Generic Equivalent (if available)

Safety

- No significant adverse drug effects such as:
  - Conjunctivitis, corneal ulcers, corneal opacities, eye pain, keratitis, photophobia, redness, swelling, and burning of the eyes
  - Painful hyperkeratotic plaques on the soles and palms
  - Liver failure
  - Porphyria
  - Leukopenia
  - Severe thrombocytopenia

Additional Requirements:

- **For Orfadin suspension:** documented inability to swallow oral solid dosage forms due to **ANY** of the following:
  - Individual is less than 5 years of age
  - Severe dysphagia
  - Esophagitis with strictures or narrowing
  - Has a feeding tube
  - Radiation therapy to head and neck for cancer

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

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Generic Equivalent (if available)

Description:

Nitisinone (Nityr, Orfadin, generic) is indicated for the treatment of individuals with hereditary tyrosinemia type 1 (HT1) in combination with dietary restriction of tyrosine and phenylalanine. Nitisinone as brand Harliku is indicated for the reduction of urine homogentisic acid (HGA) in adult individuals with alkaptonuria (AKU).

Tyrosine comes from hydrolysis of proteins from diet or from hydroxylation of phenylalanine. It is important for the synthesis of catecholamines, thyroid hormones, and melanin pigments. Normal tyrosine metabolism proceeds through 5 enzymatic steps. In step 1, tyrosine is converted to 4-hydroxyphenylpyruvate. Step 2 converts 4-hydroxyphenylpyruvate to homogentisate (or homogentisic acid). In step 3, homogentisic acid is converted to maleylacetoacetate (MAA) which in step 4 is converted to fumarylacetoacetate (FAA). In step 5, FAA is converted to fumarate and acetoacetate (or acetoacetic acid). If the last step is blocked or if there is a deficiency of the converting enzyme, MAA and FAA via an alternative pathway can be converted to toxic metabolites succinylacetoacetate (SAA) and succinylacetone (SA). SAA and SA are responsible for the observed liver and kidney toxicity. SA is also a potent inhibitor of delta-aminolevulinic acid (ALA) dehydrogenase (porphobilinogen synthase) that is involved in the first step in heme synthesis leading to accumulation of ALA, a neurotoxin responsible for the porphyric crises characteristic of HT1.

There are three sub-types of tyrosinemia, with tyrosinemia type 1 the most severe form that can have acute or chronic manifestations. World-wide incidence is estimated to be 1/100,000 to 1/120,000 and it is estimated that there are 1,000 individuals with HT1. Children with HT1 may have a characteristic odor of boiled cabbage or rotten mushrooms. Tyrosinemia type 2 is known as oculocutaneous tyrosinemia and is caused by a deficiency of tyrosine aminotransferase (TAT) the first enzyme in tyrosine metabolism. Tyrosinemia type 3 is known as primary 4-hydroxyphenylpyruvate dioxygenase (4HPPD) deficiency, the second enzyme in tyrosine metabolism, and is characterized by ataxia, seizures, mild psychomotor retardation. A fourth disorder of tyrosine metabolism occurs when there is a deficiency of homogentisic acid dioxygenase (HGD), the third enzyme of tyrosine metabolism which causes alkaptonuria. Deficiency of HGD causes formation of a brownish, blue-gray pigment that is deposited in connective tissue known as ochronosis. Individuals with this disorder also may have darkening or black urine after standing after several hours.

Hereditary tyrosinemia type 1 (HT1 or hepatorenal tyrosinemia) is a rare autosomal recessive disorder that involves the liver, kidney, and peripheral nerves. It is a well-known inborn error of metabolism and has a high incidence for the development of hepatocellular carcinoma. The natural history of the disease is liver failure, cirrhosis with hepatocellular carcinoma, end stage renal failure, acute neuropathic pain and hypertrophic cardiomyopathy. The disorder is present at birth and manifests itself within weeks or months as failure to thrive and by signs and symptoms of hepatomegaly, edema, ascites, melena, renal failure, vitamin D-resistant rickets, and hemorrhagic diathesis.

HT1 is caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the fifth enzyme of tyrosine metabolism. FAH hydrolyzes FAA into fumarate and acetoacetate. Genetic deficiency of FAH leads to cellular accumulation of FAA in lymphocytes and fibroblasts, adrenal glands, lungs, heart, some glial cells, and other cells and tissues. The liver and kidney are the two primary organs affected in individuals with HT1. The *FAH* gene is located on chromosome 15 and there are approximately 50 mutations in *FAH* gene that have been identified in different races around the world.

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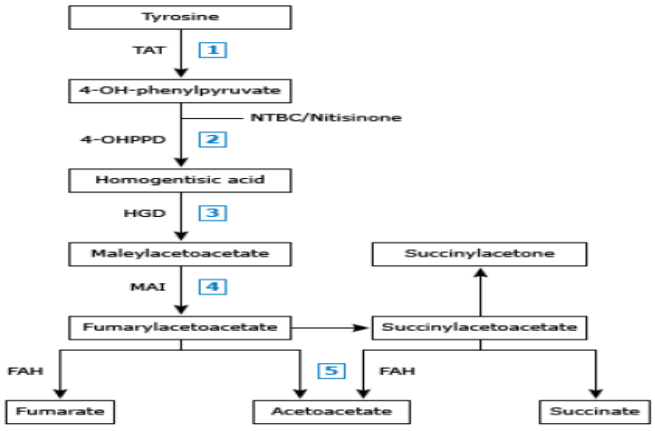
Alkaptonuria is a rare autosomal recessive disorder in which homogentisic acid accumulates and destroys connective tissue and bone, creating a condition called ochronosis. Ochronosis results in debilitating destruction of cartilage, arthritis, lumbosacral ankylosis, limitation of motion, and bone deterioration in later life. Symptoms generally begin in the third or fourth decade and progress to incapacitating spondylosis, arthropathy, and fractures by the sixth to eighth decades. Cardiac valve deterioration and renal and prostate calculi also occur.

Nitisinone, also known as 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC) is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase (4HPPD), the second enzyme in the tyrosine metabolic pathway. Nitisinone inhibits enzymatic conversion of 4-hydroxyphenylpyruvate to homogentisic acid. By inhibiting this upstream enzyme, the accumulation of FAA and MAA are prevented, and the accumulation of the toxic catabolic intermediates SA and SAA are also prevented. Treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Tyrosine degradation:



(1) Tyrosinemia type II – Corneal ulcers, hyperkeratosis, occasional intellectual disability.
(2) Tyrosinemia type III – Possible intellectual disability.
(3) Alkaptonuria – Ochronosis, black urine. Rx Nitisinone
(4) Maleylacetoacetate isomerase deficiency – Phenotype?
(5) Tyrosinemia type I – Liver failure, kidney damage. Rx Nitisinone

4-OHPPD: 4-hydroxy phenylpyruvate dioxygenase; FAH: fumarylacetoacetate hydrolase; HGD: homogentisic acid dioxygenase; MAI: maleylacetoacetate isomerase; TAT: tyrosine aminotransferase.

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Clinical manifestations of enzyme deficiencies in tyrosine catabolism					
Defective enzyme	Fumarylacetoacetate hydrolase	Tyrosine aminotransferase	4-hydroxyphenylpyruvate dioxygenase	Homogentisate dioxygenase	Maleylacetoacetate isomerase
Disease name(s)	Tyrosinemia type I Hepatorenal tyrosinemia	Tyrosinemia type II Oculocutaneous tyrosinemia Richner-Hanhardt syndrome	Tyrosinemia type III	Alkaptonuria Black urine disease	No human patients described
Elevated blood Tyrosine	++	+++	++	0	?
Ochronosis, black urine				+++	
Corneal ulcers	0	+++	+/-	0	?
Hyperkeratosis	0	++	+/-	0	?
Intellectual disability	0	+/-	+/-	0	?
Arthritis	0	0	0	+++	?
Liver failure	+++	0	0	0	?
Fanconi syndrome	++	0	0	0	?

Resources:

Harliku (nitisinone) tablets product information, revised by Cycle Pharmaceuticals Ltd. 06-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 08, 2025.

Nityr (nitisinone) tablets product information, revised by Cycle Pharmaceuticals Ltd. 05-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

Nitisinone capsule product information, revised by Analog Pharma. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

Orfadin (nitisinone) capsules product information, revised by Swedish Orphan Biovitrum AB (PUBL) 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

Orfadin (nitisinone) suspension product information, revised by Swedish Orphan Biovitrum AB (PUBL) 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

Grompe M. Disorders of tyrosine metabolism. In: UpToDate, Rand EB, Kritzer A, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated June 10, 2025. Accessed June 16, 2025.

Phornphutkul C, Introne WJ, Perry MB, et al.: Natural history of alkaptonuria. MEJM 2002 Dec 26;347(26):2111-2121. Accessed July 13, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT00107783: Long-Term Study of Nitisinone to Treat Alkaptonuria. Available from: http://clinicaltrials.gov. Last update posted August 26, 2021. Last verified December 2010. Accessed July 12, 2025.

Ranganath L, Psarelli EE, Arnoux JB, et al.: Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicenter, open-label, randomized controlled trial. Lancet Diabetes Endocrinol 2020 Sept; 8: 762–772. Accessed July 12, 2025.

Introne WJ, Perry MB, Troendle J, et al.: A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. Mol Genet Metab 2011 Aug;103 (4):307-314. Accessed July 12, 2025.