BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

**PHARMACY COVERAGE GUIDELINE**

# Nitisinone oral capsule
# NITYR™ (nitisinone) oral tablet
# ORFADIN® (nitisinone) oral capsule and oral suspension

**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 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 precertification 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.

## Criteria:

➢ **Criteria for initial therapy:** Nityr (nitisinone), Orfadin (nitisinone), or generic nitisinone is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician or Geneticist.

2. Individual has a confirmed diagnosis of hereditary tyrosinemia type 1 (HT1).

3. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Ophthalmologic examination including slit-lamp examination

b. Plasma tyrosine level
c. Serum and urine alpha-fetoprotein (AFP)
d. Urine 5-aminolevulinic acid (ALA)
e. Erythrocyte porphobilinogen (PBG) synthase activity

4. Plasma or urine succinylacetone (SA) are elevated prior to treatment.

5. Nitisinone will be used in combination with dietary restriction of tyrosine and phenylalanine.

6. Nitisinone tablets will not be used simultaneously with nitisinone capsule or suspension.

**Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Nityr (nitisinone), Orfadin (nitisinone), or generic nitisinone is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician or Geneticist.

2. Individual's condition has responded while on therapy with response defined as **BOTH** of the following:
   a. **ALL** of the following:
      i. Achieved and maintains a plasma tyrosine level below 500 micromol/L through dietary restriction of tyrosine and phenylalanine intake
      ii. Urinary succinylacetone (SA) level is less than 1 mmol/mol creatinine
      iii. Plasma SA level is less than 0.1 micromol/L
   b. **TWO** of the following:
      i. Alpha-fetoprotein (AFP) level has decreased
      ii. Urinary alpha-1 microglobulin has decreased
      iii. Urine 5-aminolevulinate (ALA) has decreased

3. Individual has been adherent with the medication and with dietary restriction of tyrosine and phenylalanine.

4. Nitisinone tablets will not be used simultaneously with nitisinone capsule or suspension.

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Conjunctivitis, corneal ulcers, corneal opacities, eye pain, keratitis, photophobia, redness, swelling, and burning of the eyes
   b. Painful hyperkeratotic plaques on the soles and palms
   c. Liver failure
   d. Porphyria
   e. Leukopenia
   f. Severe thrombocytopenia

**PHARMACY COVERAGE GUIDELINE**

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**Renewal duration**: 12 months

- 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**

## Description:

Nitisinone is indicated for the treatment of patients with hereditary tyrosinemia type 1 (HT1) in combination with dietary restriction of tyrosine and phenylalanine.

Tyrosine comes from hydrolysis of proteins from the 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 patients 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 patients 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.

Nitisinone, also known as 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC) is 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.

## Resources:

Nitisinone capsule product information, revised by Par Pharmaceutical, Inc. 10-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 12, 2022.

Nityr (nitisinone) tablets product information, revised by Cycle Pharmaceuticals Ltd. 06-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 12, 2022.

Orfadin (nitisinone) capsules and suspension product information, revised by Swedish Orphan Biovitrum AB (PUBL) 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 12, 2022.

Grompe M. Disorders of tyrosine metabolism. In: UpToDate, Hahn S, Rand EB, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on November 13, 2020. Accessed July 12, 2022.