



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 7/21/2016
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

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

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Nityr (nitisinone), Orfadin (nitisinone), and nitisinone is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Prescriber is a physician specializing in the patient's diagnosis or is consultation with a Pediatrician or Geneticist
 2. A confirmed diagnosis of hereditary tyrosinemia type 1 (HT1)
 3. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring 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), and nitisinone is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is consultation with a Pediatrician or Geneticist
 2. Individual's condition has responded while on therapy
 - a. Response is defined as **BOTH** of the following:
 - i. **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
 - ii. **TWO** of the following:
 1. Alpha-fetoprotein (AFP) level has decreased
 2. Urinary alpha-1 microglobulin has decreased
 3. Urine 5-aminolevulinic acid (ALA) has decreased

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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
 - a. Significant adverse effect such as:
 - i. Conjunctivitis, corneal ulcers, corneal opacities, eye pain, keratitis, photophobia, redness, swelling, and burning of the eyes
 - ii. Painful hyperkeratotic plaques on the soles and palms
 - iii. Liver failure
 - iv. Porphyria
 - v. Leukopenia
 - vi. Severe thrombocytopenia

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 a Non-cancer Medications**
2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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

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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-methylbenzoyl)-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 on July 30, 2021.

Nityr (nitisinone) tablets product information, revised by Cycle Pharmaceuticals Ltd. 06-2021. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 30, 2021.

Orfadin (nitisinone) capsules and suspension product information, revised by Swedish Orphan Biovitrum AB (publ) 05-2019. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 30, 2021.

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>. Accessed on July 31, 2021.
