BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/21/16**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

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.

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) and Orfadin (nitisinone) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a specialist with knowledge and expertise in metabolic diseases or genetic diseases

  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:
     - Ophthalmologic examination including slit-lamp examination
     - Plasma tyrosine level
     - Serum and urine alpha-fetoprotein (AFP)
     - Urine 5-aminolevulinic acid (ALA)
     - Erythrocyte porphobilinogen (PBG) synthase activity
     - Comprehensive metabolic panel
     - Complete blood count with differential

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

  5. Nityr or Orfadin will be used in combination with dietary restriction of tyrosine and phenylalanine

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nityr (nitisinone) and Orfadin (nitisinone) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Continues to be seen by specialist with knowledge and expertise in metabolic diseases or genetic diseases

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

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

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4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use, 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

Renewal duration: 12 months

Description:

Nityr (nitisinone) and Orfadin (nitisinone) are 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

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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.

Nityr (nitisinone) and Orfadin (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:

Nityr. Package Insert. Revised by manufacturer 07/2017. Accessed 09-01-2017, 07-19-2018.

Orfadin. Package Insert. Revised by manufacturer 09/2017. Accessed 07-19-2018.

Orfadin. Package Insert. Revised by manufacturer 02/2017. Accessed 06-28-2017.

Orfadin. Package Insert. Revised by manufacturer 04/2016. Accessed 05-19-2016.

Nelwan M. The Tyrosinemia Type I. Advances in Life Sciences and technology 2012; 14: 7-19

Bijarnia S, Puri RD, Ruel J, et al.: Tyrosinemia Type I – Diagnostic Issues and Prenatal Diagnosis. Indian J Pediatrics 2006; 73(2): 163-165

UpToDate: Disorders of tyrosine metabolism. Current through Jul 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/disorders-of-tyrosine-metabolism?search=hereditary%20tyrosinemia%20type%201&source=search_result&selectedTitle=1~37&usage_type=default&display_rank=1

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.