**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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**Description:**

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

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 symptoms of hepatomegaly, edema, ascites, melena, renal failure, vitamin D-resistant rickets, and hemorrhagic diathesis.

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.

HT1 is caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the fifth enzyme of tyrosine metabolism. FAH hydrolyzes fumarylacetoacetate (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.

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 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.

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.

Definitions:

**Drug related events:**

Ineffective / failure

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is
documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

**Allergic reaction / hypersensitivity** – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

**Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

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**Precertification**:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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](http://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.
ORFADIN® (nitisinone) oral capsule and oral suspension (cont.)

**Criteria:**

See “Resources” section for FDA-approved dosage.

- Precertification for Orfadin requires completion of the specific request form in its entirety. 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 Pharmacy precert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Orfadin is considered **medically necessary** when ALL of the following criteria are met:
  1. Prescriber is a specialist with knowledge and expertise in metabolic diseases or genetic diseases
  2. Medical record documentation of a confirmed diagnosis of hereditary tyrosinemia type 1 (HT1)
  3. Orfadin will be used in combination with dietary restriction of tyrosine and phenylalanine
  4. ALL of the following baseline tests have been completed before initiation of treatment:
     - Ophthalmologic examination including slit-lamp examination
     - Plasma tyrosine levels
     - Plasma and urine succinylacetone
     - Urine 5-aminolevulinic acid (ALA)
     - Serum and urine alpha-fetoprotein
     - Comprehensive metabolic panel
     - Complete blood count with differential
     - Erythrocyte porphobilinogen (PBG) synthase activity

- Orfadin for all other indications not previously listed is considered **experimental or investigational** based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Hereditary tyrosinemia type 2 also known as oculocutaneous tyrosinemia or Richner-Hanhart syndrome
- Hereditary tyrosinemia type 3
- Alkaptonuria
- Transient tyrosinemia of the newborn
- Hepatocellular dysfunction of any etiology
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Criteria Revisions:

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Resources:


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


FDA-approved indication and dosage:

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<th>Indication</th>
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| ORFADIN is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. | • The recommended initial dosage is 0.5 mg/kg orally twice daily.  
• Titrate the dose based on biochemical and/or clinical response, as described in the full prescribing information.  
• The maximum dosage is 1 mg/kg orally twice daily.  
Preparation and Administration Instructions:  
• For instructions on preparing, measuring and administering the oral suspension, see the full prescribing information  
• Maintain dietary restriction of tyrosine and phenylalanine  
• Take ORFADIN capsules at least one hour before, or two hours after a meal  
• For patients who have difficulties swallowing capsules and who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use  
• Take ORFADIN oral suspension without regard to meals |