Orfadin is a 4-Hydroxyphenylpyruvate Dioxygenase Inhibitor used for the treatment of hereditary tyrosinemia type 1 (HT-1). In patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine accumulate and cause liver and kidney toxicity. Nitisinone competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites.

**Pre-Authorization Criteria:**
Orfadin is prescribed in the treatment of hereditary tyrosinemia type 1 (HT-1) as an adjunct to dietary restriction of tyrosine and phenylalanine.
Orfadin must be used with dietary restriction of tyrosine and phenylalanine; inadequate restriction can result in toxic effects to the eyes, skin, and nervous system. Evaluate plasma tyrosine concentrations in patients who develop signs and symptoms of toxicity. Nutritional consultation is required.

VCHCP requires that Orfadin be prescribed by a physician specializing in the condition being treated.

**Prescribing and Access Restrictions:**
Distributed by Rare Disease Therapeutics, Inc; for information regarding acquisition of product, call Accredo Health Group, Inc at 1-888-454-8860

**Dosing: Adult:**
Note: Must be used in conjunction with a diet restricted in tyrosine and phenylalanine.
HT-1: Oral: Initial: 1 mg/kg/day in 2 divided doses
Dosing adjustment for inadequate response: Note: Inadequate response is defined as continued abnormal biological parameters (erythrocyte PBG-synthase activity, urine 5-ALA, and urine succinylacetone) despite treatment. If the aforementioned parameters are not available, may use urine succinylacetone, liver function tests, alpha-fetoprotein, serum tyrosine, and serum phenylalanine to evaluate response (exceptions may include during initiation of therapy and exacerbations).
*Abnormal biological parameters at 1 month:* Increase dose to 1.5 mg/kg/day
*Abnormal biological parameters at 3 months:* Further increase to maximum dose of 2 mg/kg/day

**Dosing: Pediatric:**
Note: Must be used in conjunction with a diet restricted in tyrosine and phenylalanine.
HT-1: Oral: Infants and Children: Refer to adult dosing.

Dosing: Geriatric:
Refer to adult dosing.

Dosing: Renal Impairment:
No dosage adjustment provided in manufacturer’s labeling (has not been studied).

Dosing: Hepatic Impairment:
No dosage adjustment provided in manufacturer’s labeling (has not been studied).

Dosage Forms: U.S.:
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Capsule, Oral:
Orfadin: 2 mg, 5 mg, 10 mg

Generic Equivalent Available: U.S.-No

Administration:
Administer in 2 divided doses in the morning and evening at least 1 hour prior to, or 2 hours after a meal. Dose does not need to be split evenly; divide total dose as to limit the number of total capsules administered at each administration. Capsules may be opened and contents suspended in a small quantity of water, formula, or apple sauce; use immediately.

Adverse Reactions:
Alopecia, dry skin exfoliative dermatitis, rash, pruritus, thrombocytopenia, leukopenia, epistaxis, granulocytopenia, porphyria, hepatic neoplasm, hepatic failure, conjunctivitis, corneal opacity, dermatitis, photophobia, blepharitis, cataracts, eye pain
Other Serious Less Common Reactions: abdominal pain, brain tumor, corneal ulceration, cyanosis, encephalopathy, gastrointestinal hemorrhage, hepatic dysfunction, hyperkinesias, hypoglycemia, melena, pathologic fracture, respiratory insufficiency, seizure, septicemia, somnolence.

References:

### Revision History:

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Date Approved by P&T Committee: 1/23/18  
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Date Approved by P&T Committee: 1/22/19  
Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD  
Date Approved by P&T Committee: 2/18/20

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