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:**
Treatment of hereditary tyrosinemia type 1 (HT-1) as an adjunct to dietary restriction of tyrosine and phenylalanine-containing foods.

**NOTE:** 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.

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

**NOTE:** 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.

Oral: Initial: 0.5 mg/kg/day in 2 divided doses; may be administered once daily (eg, 1 to 2 mg/kg once daily) if serum and urine succinylacetone is undetectable after ≥4 weeks of therapy; maximum dose: 2 mg/kg/day; administer in 2 divided doses in the morning and evening at least 1 hour prior to, or 2 hours after a meal
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

Dosage Forms: U.S.:
Capsule: 2 mg, 5 mg, 10 mg

Adverse Reactions:
Increased plasma tyrosine; 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

References:
5. www.uptodate.com: Nitisinone: Drug Information
6. Orfadin (nitisinone) [prescribing information]. Waltham, MA: Sobi Inc; May 2019.

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