GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

1. Does the patient have a documented diagnosis of hereditary tyrosinemia type 1 (HT-1) AND meets ALL of the following criteria?
   • The patient has elevated urinary or plasma succinylacetone (SA) levels OR a mutation in the fumarylacetoacetate hydrolase (FAH) gene
   • The medication is being prescribed by or given in consultation with a prescriber specializing in inherited metabolic diseases
   • The patient has been counseled on maintaining dietary restriction of tyrosine and phenylalanine

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at end of guideline.

2. Is the request for Orfadin capsules?

   If yes, approve for 6 months by GPID.
   APPROVAL TEXT: Renewal requires that the patients urinary or plasma succinylacetone (SA) levels have decreased from baseline while on treatment with nitisinone.
   If no, continue to #3.

3. Is the request for Orfadin suspension and has the patient tried Orfadin capsules?

   If yes, approve for 6 months by GPID.
   APPROVAL TEXT: Renewal requires that the patients urinary or plasma succinylacetone (SA) levels have decreased from baseline while on treatment with nitisinone.
   If no, do not approve.
   DENIAL TEXT: See the denial text at end of guideline.

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NITISINONE

GUIDELINES FOR USE (CONTINUED)

DENIAL TEXT: The guideline named NITISINONE (Orfadin) requires a documented diagnosis of hereditary tyrosinemia type 1 (HT-1) as confirmed by elevated urinary or plasma succinylacetone (SA) levels or a mutation in the fumarylacetoacetate hydrolase (FAH) gene. In addition, the following criteria must also be met:
• The medication must be prescribed by or given in consultation with a prescriber specializing in inherited metabolic diseases.
• The patient must be counseled on maintaining dietary restriction of tyrosine and phenylalanine.
• For requests of Orfadin oral suspension, the patient must have tried Orfadin capsules. For patients who have difficulties swallowing capsules, Orfadin capsules may be opened and the contents suspended in a small amount of water, formula, or applesauce immediately before use.

RENEWAL CRITERIA

1. Does the patient have a diagnosis of hereditary tyrosinemia type 1 AND meets the following criteria?
• The patients urinary or plasma succinylacetone (SA) levels have decreased from baseline while on treatment with nitisinone.

If yes, approve for 12 months by GPID.
If no, do not approve.

DENIAL TEXT: The guideline named NITISINONE (Orfadin) renewal requires urinary or plasma succinylacetone (SA) levels that have decreased from baseline while on treatment with nitisinone.

RATIONALE
Promote appropriate utilization of NITISINONE based on FDA approved indication.

FDA APPROVED INDICATION
Orfadin (nitisinone) 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.

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NITISINONE

FDA APPROVED INDICATION (CONTINUED)

BACKGROUND
Hereditary tyrosinemia type 1 (HT-1), also known as hepatorenal tyrosinemia, is the most severe of the tyrosine metabolism disorders, occurring in 1 in 12,000 to 1 in 100,000 individuals of northern European descent. HT-1 is an autosomal recessive disorder caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme in the pathway of tyrosine catabolism. Fumarylacetoacetate (FAA), the substrate of FAH, accumulates in hepatocytes and proximal renal tubular cells and causes damage to liver and kidney cells. The resultant damage impairs several metabolic processes (e.g., gluconeogenesis, ammonia detoxification, protein synthesis) and increases the risk for hepatocellular carcinoma (HCC), occurring in as many as 37% of untreated patients older than 2 years of age. Elevated tyrosine levels are also commonly observed, and while tyrosine is not toxic to the liver or kidneys, it can cause dermatologic, ophthalmologic, and possibly neurodevelopmental problems.

Detection of succinylacetone (SA: the principal metabolite of FAA) in urine, blood, or amniotic fluid is the most reliable diagnostic test for HT-1. Genetic testing for disease-causing mutations is also available and may be useful for prenatal diagnosis and reproductive counseling, but is not essential for clinical management.

HT-1 is characterized by severe progressive liver disease and renal tubular dysfunction. Most patients present in early infancy with failure to thrive and hepatomegaly. The progression of liver disease can be chronic or acute, with rapid deterioration and early death. If untreated, patients with HT-1 have a significantly shortened lifespan. Patients may die of acute liver failure before the second year after birth or from chronic liver failure or HCC before the end of the second decade.

Patients are managed with strict dietary restrictions, but this alone does not prevent the production of SA, prevent the progression of liver or renal disease, or reduce the risk of developing HCC and neurologic abnormalities.

Orfadin is the medical treatment of choice for HT-1. Orfadin is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, which limits the formation of toxic metabolites such as FAA and SA. Historically, approximately 90% of patients treated with Orfadin have experienced clinical improvement. Early initiation of Orfadin treatment also reduces the risk of developing HCC and the need for liver transplantation.

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NITISINONE

FDA APPROVED INDICATION (CONTINUED)

EFFICACY

The efficacy of Orfadin was evaluated in an open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 years (median age 9 months) at the time of enrollment. All patients were treated with Orfadin at a starting dose of 0.3-0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg twice daily based on biochemical and clinical response. Efficacy was assessed by comparing survival and incidence of liver transplant to historical controls.

Median duration of treatment was 22 months (range <1 month to 80 months). Results are presented in Table 1. The long-term effect of Orfadin on hepatic function was not assessed in the clinical trial.

Table 1. Survival probabilities compared to historical controls [from Orfadin Prescribing Information]

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Survival probabilities</th>
<th>Orfadin</th>
<th>Historical controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year</td>
<td>88%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>4 year</td>
<td>88%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>2-6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year</td>
<td>94%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>4 year</td>
<td>94%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

The effects on urine and plasma SA were also assessed in this study.
- Among patients with measured urine SA (n=186), urine SA levels decreased to < 1mmol/mol creatinine in all patients, with median time to normalization of 0.3 months. The recurrence probability of an abnormal urine SA value was 1% at an Orfadin concentration of 37 μmol/L (95% CI: 23, 51 μmol/L).
- Among patients with measured plasma SA, plasma SA levels decreased to < 0.1 μmol/L in 87% (150/172) of patients, with median time to normalization of 3.9 months.

Porphyria-like crises are commonly reported in patients with HT-1 who are not treated with Orfadin. During the clinical study, porphyria-like crisis was reported in 3 patients (0.3% cases per year), compared to an expected incidence of 5 to 20% cases per year as part of the natural history of HT-1.

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NITISINONE

FDA APPROVED INDICATION (CONTINUED)

SAFETY
There are no contraindications with Orfadin. Orfadin has warnings for elevated plasma tyrosine levels, ocular symptoms, developmental delay, hyperkeratotic plaques; leukopenia and severe thrombocytopenia. Treatment with Orfadin may cause an increase in plasma tyrosine levels, which at levels > 500 μmol/L may lead to ocular signs and symptoms (e.g., corneal ulcers, corneal opacities, conjunctivitis, keratitis, eye pain, photophobia), varying degrees of intellectual disability and developmental delay, and painful hyperkeratotic plaques on the soles and palms. Ophthalmologic examination should be performed prior to initiating Orfadin treatment; patients who develop ocular adverse reactions or exhibit an abrupt change in neurologic status should undergo ophthalmologic reexamination and immediate measurement of plasma tyrosine concentrations. Orfadin dosing should not be adjusted in order to lower plasma tyrosine concentrations; concomitant restriction of dietary tyrosine and phenylalanine should be maintained and dietary intake reassessed. Transient leukopenia and thrombocytopenia were also observed in patients treated with Orfadin; platelet and white blood cell counts should be monitored during Orfadin therapy.

The oral suspension contains a unique warning for adverse reactions caused by glycerol, an inactive ingredient of this formulation. Oral doses of glycerol of 10 grams or more (contained in single doses of Orfadin more than 20 mL) have been reported to cause headache, upset stomach, and diarrhea; patients who are unable to tolerate the suspension should consider switching to capsules.

The most common adverse reactions were elevated tyrosine levels (>10%), thrombocytopenia (3%), leukopenia (3%), conjunctivitis (2%), corneal opacity (2%), keratitis (2%), photophobia (2%), eye pain (1%), blepharitis (1%), cataracts (1%), granulocytopenia (1%), epistaxis (1%), pruritus (1%), exfoliative dermatitis (1%), dry skin (1%), maculopapular rash (1%), and alopecia (1%).

There are limited human data evaluating Orfadin in pregnancy or lactation. In animal reproduction studies with mice, Orfadin given at doses 0.4 times the recommended human dose caused incomplete skeletal ossification of fetal bones and decreased pup survival. In rabbits, Orfadin caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 1.6 times the recommended human dose. Animal data also suggest that Orfadin is present in rat milk due to findings of ocular toxicity and lower body weight in drug-naïve nursing rat pups.

The clinical trial assessing the safety and efficacy of Orfadin involved only pediatric patients ages birth to 17 years and did not include any subjects aged 65 years and older. While no pharmacokinetic studies of Orfadin have been performed in geriatric patients, dose selection for an elderly patient should be cautious due to the greater frequency of decreased hepatic, renal, and cardiac function, and concomitant disease or other drug therapy in this patient population.

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NITISINONE

FDA APPROVED INDICATION (CONTINUED)

Orfadin may inhibit CYP2C9 and potentially increase systemic exposure of CYP2C9 substrates (e.g., ibuprofen, losartan, montelukast, sulfamethoxazole), and co-administration of these drugs may warrant additional monitoring.

DOSAGE

Recommended Dosage:
- The recommended initial dosage is 0.5 mg/kg orally twice daily.
- Titrate the dose based on biochemical and/or chemical 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 applesauce immediately before use.
- Take Orfadin oral suspension without regard to meals.

DOSAGE FORMS AND STRENGTHS

- Capsules: 2 mg, 5 mg, 10 mg, 20 mg
- Oral suspension: 4 mg/mL

REFERENCES


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Effective: 03/01/18