Drug Monograph

Drug/Drug Class:	**Orfadin® (nitisinone) capsule/ Tyrosinemia Agents**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Orfadin® is now available in a capsule containing 20 mg nitisinone. Manufacturer: Sobi, Inc., Waltham, MA 02451
Summary of Findings:	Orfadin® was evaluated in an open label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 years at enrollment. Dietary restriction in combination with nitisinone resulted in a significantly higher survival probability when compared to treatment with dietary restriction alone. Also, urine succinylacetone was measured in 186 patients. In all 186 patients, urinary succinylacetone level decreased to less than 1 mmol/mol creatinine. Porphyria-like crisis were reported in 3 patients (0.3% of cases per year) during the clinical study compared to an incidence of 5 to 20% of cases pere year expected as part of the natural history of the disorder. After one year of treatment in a subgroup of patients, overall median alpha-1 microglobulin decreased by 1.5 grams/mol creatinine.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Hereditary tyrosinemia type 1 (HT-1) is a rare pediatric disease. It is a genetic metabolic disorder that results from an inability to break down the amino acid tyrosine. Because of resulting liver failure and liver cancer, children with HT-1 rarely survive into their twenties without a liver transplant. HT-1 affects approximately 1 in 100,000 babies.

Dosage Form(s) [1]

Orfadin® is now available in a capsule containing 20 mg nitisinone.

Manufacturer [1]

Sobi, Inc., Waltham, MA 02451

Indication(s) [1]

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

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Orfadin® is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, Orfadin® prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity.

Pharmacokinetics:

	Orfadin®
Protein binding	> 95%
Metabolism	Liver, Minor metabolism possibly mediated by CYPA3A4 enzyme.
Excretion	Not known
Half life	54 hours

STUDY DESIGN	Open-label, uncontrolled study.
INCLUSION CRITERIA	Diagnosis of HT-1 (diagnosed by the presence of succinylacetone in the urine or plasma), age 0-22 years at enrollment.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were treated with Orfadin at a starting dose of 0.6 to 1 mg/kg/day, and the dose was increased in some patients to 2 mg/kg/day based on weight, liver and kidney function tests, platelet count, serum amino acids, urinary phenolic acid, plasma and urine succinylacetone, erythrocyte PBG-synthase, and urine 5-ALA. The median duration of treatment was 22 months.
RESULTS	Patients presenting with HT-1 younger than 2 months of age who were treated with dietary restriction and Orfadin, 2 and 4 year survival probabilities were 88% and 88% respectively. This was compared to only 29% in patients treated with dietary restriction alone. For patients presenting between 2 and 6 months of age who were treated with dietary restrictions and Orfadin, 2 and 4 year survival probabilities were 94% and 94%. This was compared to historical controls that showed that patients treated with dietary restriction alone had 2 and 4 year survival probabilities of 74% and 60% respectively.
SAFETY	Not specified.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Elevated plasma tyrosine levels, ocular symptoms, developmental delay and hyperkeratotic plaques
- Leukopenia and severe thrombocytopenia

Adverse Effects [(1)]

Most common, ≥ 2 %	**Orfadin® (n=207)**
Elevated tyrosine levels	>10%
Leukopenia	3%

Thrombocytopenia	3%
Conjunctivitis	2%
Corneal opacity	2%
Keratitis	2%
Photophobia	2%

Drug Interactions [(1)]

- CYP2C9 substrates

Dosage and Administration [(1)]

The FDA recommended starting dose is 0.5 mg/kg orally twice daily. Titrate the dose for individual patients, as needed based on biochemical and/or clinical response.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH*
Nitisinone	Orfadin	Sobi	20 mg capsule	1 capsule twice daily	$50,493.60

* Maximum Allowable Cost

Conclusion

Orfadin® is indicated for the treatment of patients with hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine. An open-label clinical study showed that Orfadin treatment plus dietary restrictions resulted in a 2 year and 4 year survival probability of 88% for children less than two months of age at the time of HT-1 diagnosis. This is compared to historical data controls that showed patients of the same age that were treated with dietary restriction alone have survival probabilities of only 29%. For patients presenting between 2 months and 6 months of age, who were treated with dietary restrictions and Orfadin, 2 and 4 year survival probabilities were 94%. This is compared to historical data controls that showed patients of the same age group that were treated with dietary restriction alone had 2 year and 4 year survival probabilities of 74% and 60%.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1. Orfadin. Retrieved 11/25/2016 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d449b73-d503-4132-b978-d890491975df
2. Orfadin. Retrieved 11/25/20160 from http://www.centerwatch.com/drug-information/fda-

approved-drugs/drug/765/orfadin-nitisinone

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