Drug Monograph

Drug/Drug Class:	**Endari® (L-glutamine) powder for solution/ Sickle Cell**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **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:	Endari® is supplied in paper-foil-plastic laminate packets containing 5 grams of L-glutamine powder. Manufactured for: Emmaus Medical, Inc., Torrance, CA 90503
Summary of Findings:	Efficacy was established in a Phase 3 randomized, placebo-controlled clinical trial in 230 patients 5 to 58 years of age with sickle cell anemia or sickle beta-thalassemia, including 46 children 5 to 11 years old and 64 adolescents 12 to 17 years old. Patients receiving Endari had a median number of 3 sickle cell crisis over 48 weeks compared to 4 with placebo, a median number of 2 hospitalizations for sickle cell pain compared to 3, 6.5 cumulative days in hospital compared to 11, 8.6% occurrences of acute chest syndrome compared with 23.1%, and a median of 84 days to first crisis compared to 54 days. Overall, Endari reduced the average cumulative crisis by 25%.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ No PA Required

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]

Sickle cell disease is a genetic condition. People who have it inherited certain hemoglobin genes from their parents. Hemoglobin is the protein inside of red blood cells that carries oxygen. Abnormal hemoglobin makes the red blood cells sickle shaped.

Patients with sickle cell disease can have pain crises that may last a few hours, a few days, or sometimes longer. Cold, stress, or dehydration can bring on pain.

Patients with sickle cell disease can have problems that need immediate care by a doctor such as; acute chest syndrome, aplastic crisis, hand-foot syndrome, infection, priapism, splenic sequestration crises, and stroke. Patients with sickle cell are also at risk for problems such as leg ulcers, bone or joint damage, gallstones, kidney damage, eye damage, and delayed growth.

Dosage Form(s) [1]

Endari® is supplied in paper-foil-plastic laminate packets containing 5 grams of L-glutamine powder.

Manufacturer [1]

Manufactured for: Emmaus Medical, Inc., Torrance, CA 90503

Indication(s) [1]

Endari® is indicated to reduce acute complications of sickle cell disease in patients 5 years or older.

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

The mechanism of action of L-glutamine in sickle cell disease is unknown, but may be due to increased availability of reduced glutathione for regulating and preventing oxidative damage in red blood cells.

Pharmacokinetics:

	Endari®
Volume of Distribution	200 ml/kg
Metabolism	Involved in metabolic activities such as formation of glutamate, proteins, nucleotides, and amino sugars
Elimination	Via glomerular filtration but is completely reabsorbed
Half-life	1 hour

Phase 3 Trial

STUDY DESIGN	Randomized, double-blind, placebo-controlled, multicenter, Phase 3 clinical trial (N=230)
INCLUSION CRITERIA	Patients, 5 to 58 years of age, with sickle cell anemia or sickle beta-thalassemia and at least 2 painful crises within the previous year.
EXCLUSION CRITERIA	Patients who received blood products within the previous 3 weeks or had renal or hepatic insufficiency.
TREATMENT REGIMEN	Patients were randomized to receive Endari or placebo for 48 weeks, followed by 3 weeks of tapering. Patients who had been stabilized on hydroxyurea continued therapy throughout the study.
RESULTS	Patients receiving Endari had a median number of 3 sickle cell crises over 48 weeks compared to 4 for those patients receiving placebo. The median number of hospitalizations for sickle cell pain was 2 in the Endari group compared with 3 in the placebo group. The cumulative days in hospital (6.5 vs. 11 days) and occurrences of acute chest syndrome (8.6% vs. 23.1% of patients) were also decreased, while median time to first crisis was longer (84 days vs. 54 days) in the Endari group versus placebo.
SAFETY	Not specified.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- None

Adverse Effects [(1)]

Most common, > 10%	**Endari® (n=187)**	**Placebo (n=111)**
Constipation	21%	18%
Nausea	19%	14%
Headache	18%	15%

Abdominal pain	17%	16%
Cough	16%	14%
Pain in extremity	13%	7%
Back pain	12%	5%
Chest pain	12%	8%

Drug Interactions [(1)]

- Drug interaction studies have not been concluded

Dosage and Administration [(1)]

The FDA recommended dose is 5 grams orally twice daily in patients weighing less than 30 kg, 10 grams twice daily for 30 to 65 kg, and 15 grams twice daily for weight greater than 65 kg. Mix with 8 ounces of cold or room temperature beverage or with 4 to 6 ounces of food immediately before ingestion; complete dissolution of powder is not necessary.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH**
L-glutamine	Endari	Emmaus Medical	5 gram packet	5 grams twice daily	$1,105.20
			5 gram packet	10 grams twice daily	$2,210.40
			5 gram packet	15 grams twice daily	$3,315.60
Hydroxyurea	Hydrea	Bristol-Myers Squibb	500 mg capsule	500 mg daily	$10.80
			500 mg capsule	1,000 mg daily	$21.60

** Maximum Allowable Cost

Conclusion

Endari® is only the second agent in adults and the first agent in pediatrics to be approved for the reduction of acute complications of sickle cell disease. Endari® received orphan product designation for the treatment of rare disease. It is indicated in patients 5 years or older. In a phase 3 clinical trial, patients receiving Endari had a lower median number of sickle cell crises over 48 weeks, a lower median number of hospitalizations for sickle cell pain, fewer cumulative days in the hospital, fewer occurrences of acute chest syndrome, and a longer median time to first crisis. Compared with placebo, Endari reduced the average cumulative crisis count by 25%. The most common adverse events are constipation, nausea, headache, abdominal pain, and cough.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Product Information: Endari™, L-glutamine oral powder. Emmaus Medical, Inc, Torrance, CA, 07/2017.
2) Sickle Cell Disease. Retrieved 5/24/2018 from https://kidshealth.org/en/parents/sickle-cell-anemia.html

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