Endari (L-glutamine) MNR
Policy Number: C18364-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
04/23/2020	3/17/2021	4/26/2022
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
NA	RxPA	Q2 2021 20210428C18364-A

PRODUCTS AFFECTED:
Oral (Powder for suspension)

DRUG CLASS:
Amino acid

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy- US Bioservices- Limited Pharmacy

AVAILABLE DOSAGE FORMS:
5-gram L-glutamine powder packet

FDA-APPROVED USES:
Reduce the acute complications of sickle cell disease (SCD) in adult and pediatric patients 5 years of age and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Sickle Cell Disease

REQUIRED MEDICAL INFORMATION:
A. SICKLE CELL DISEASE

1. Documented diagnosis of sickle cell disease with baseline number of crises per year
   AND
2. Chart note documentation confirms sickle cell disease and meets the following characteristics: 2 or more ACUTE pain crises in a 12-month period requiring emergency room/medical facility treatment with a parenterally administered narcotic or parenterally administered ketorolac OR recurrent of acute chest syndrome [DOCUMENTATION REQUIRED]
   AND

3. Prescriber attestation that member has tried and failed OTC/other available L-glutamine products
   AND
4. Documentation of member's weight within that last 30 days
   AND
5. (a) Member has had an inadequate response to an adherent, maximally tolerated dose of Hydroxyurea for the past 180 days.
   OR
   (b)Justification provided regarding intolerance or contraindication to the use of Hydroxyurea

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 6 months

QUANTITY:
Maximum of 6 packets per day, max of 30 days per fill

Weight (kg)	Weight (lb.)	Per dose in grams	Per day in grams	Packets per dose	Packets per day
Less than 30	Less than 66	5	10	1	2
30 to 65	66 to 143	10	20	2	4
Greater than 65	Greater than 143	15	30	3	6

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a physician who specializes in SCD

AGE RESTRICTIONS:
5 years of age and older

CONTINUATION OF THERAPY:
A. SICKLE CELL DISEASE
1. Member has had a reduction in the number of crisis and/or acute chest syndrome episodes since initiating therapy.
   AND
2. Member continues on an FDA approved dose.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of Endari (L-glutamine) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. No contraindications to report at this time. Use with caution in members with hepatic and/or renal impairment. No specific dosage adjustments are documented. Safety has not been established in members younger than 5 years old. No clinical benefit observed as measured by a reduction in the number of sickle cell crises or maintained improvement when compared history before initiation of Endari.

OTHER SPECIAL CONSIDERATIONS:
There is no high-quality evidence and no head-to-head studies from published clinical trials and peer-reviewed literature evaluating the clinical safety and efficacy of this pharmaceutical grade L-glutamine oral powder versus over-the-counter L-glutamine, which is separately available as a nutritional supplement and widely available without a prescription at drugstores across the United

States, although in much smaller doses than those the FDA recommends for sickle cell disease.

There is also limited evidence from published clinical trials and lack of data supporting the long-term benefits, side-effect profile, or risks associated with pharmaceutical grade L-glutamine (Endari) over the various L-glutamine dietary supplements. In addition, there is also no head-to-head studies with hydroxyurea, the only previous drug treatment available for the management of SCD.

Currently, it may be considered as add-on therapy in patients ages 5 years and older who have at least two sickle cell crises a year, despite maximally tolerated hydroxyurea doses, or as monotherapy for patients unable to tolerate hydroxyurea.

BACKGROUND:

SCD is a group of inherited red blood cell disorders.[3] Healthy red blood cells are round, and they move through small blood vessels to carry oxygen to all parts of the body.[3] In someone who has SCD, the red blood cells become hard and sticky and look like a C-shaped farm tool called a "sickle".[3] The sickle cells die early, which causes a constant shortage of red blood cells.[3] Also, when they travel through small blood vessels, they get stuck and clog the blood flow.[3] This can cause pain and other serious problems such infection, acute chest syndrome and stroke.[3]

SCD affects millions of people worldwide and is most common in people with African heritage.[4] In the United States, about 100,000 Americans have SCD with a prevalence of 1 in 2,500 newborns, 1 in 365 African Americans and 1 in 36,000 Hispanic births.[4] In the pathogenesis of SCD, the following are responsible for the various clinical manifestations: impaired circulation, destruction of RBCs, stasis of blood flow and ongoing inflammatory responses.[4]

Administration of routine immunizations is crucial preventive care in managing SCD.[4] Impaired splenic function increases susceptibility to infection.[4] Children 6 months and older and adults with SCD should receive influenza vaccine annually.[4] Reduced mortality has been associated with the introduction of pneumococcal vaccines.[4] The risk of meningococcal disease is also higher in SCD and vaccination is recommended for individuals with functional or acquired asplenia.[4]

The only other available treatments have been hydroxyurea and chronic transfusions.[1] Hydroxyurea, which increases fetal hemoglobin levels, has reduced the number of painful crises (median 2.5/year vs 4.5/year with placebo), hospitalizations for sickle cell pain (median 1.0/year vs 2.4/year with placebo), and patients who required transfusions (median 48 vs 73 with placebo).[1] In a 17.5-year trial, it also appeared to improve survival without causing serious adverse effects.[1]

Endari (L-glutamine) is an amino acid indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. FDA approval of Endari was based on the results of a 48-week, double-blind trial, available only as an abstract, in 230 patients 5-58 years old with sickle cell anemia or sickle β-thalassemia who had experienced ≥2 painful crises within the past 12 months.[1] Patients were randomized to receive L-glutamine 0.3 g/kg or placebo twice daily; those who had been on stable doses of hydroxyurea for at least 3 months (about 66% in both groups) could continue taking it.[1] The median number of sickle cell crises during the 48 weeks of the trial, the primary endpoint, was 3 with L-glutamine versus 4 with placebo, a statistically significant difference.[1] Treatment with L-glutamine also reduced the median number of hospitalizations for sickle cell pain and increased the median time to first painful crisis.[1]

APPENDIX:

None

REFERENCES:

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3. Chan C, Frei-Jones M. Sickle Cell Disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR,Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill
4. A Phase Iii Safety and Efficacy Study Of L-glutamine To Treat Sickle Cell Disease or SickleBo-thalassemia - Full Text View https://clinicaltrials.gov/ct2/show/NCT01179217
5. Endari (L-glutamine) oral powder package insert. Torrance, CA: Emmaus Medical, Inc.; 2017July
6. U.S. Food and Drug Administration. FDA approved L-glutamine powder for the treatment of sickle cell disease. U.S. Food and Drug Administration: Approved Drugs. July 7, 2017; Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566097.htm. Accessed March 2020.
7. Sickle cell disease. Genetics Home Reference. August 2012; http://ghr.nlm.nih.gov/condition/sickle-cell-disease.