Original Effective Date: 04/23/2020
Current Effective Date: 06/28/2025
Last P&T Approval/Version: 04/30/2025
Next Review Due By: 04/2026
Policy Number: C18364-A

Endari (L-glutamine) MNR

PRODUCTS AFFECTED

Endari (L-glutamine), L-glutamine

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Sickle Cell Disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. SICKLE CELL DISEASE:
   1. Documented diagnosis of sickle cell disease
      AND
   2. Documentation of baseline number of crises per year

AND

3. Documentation member has ONE of the following [DOCUMENTATION REQUIRED]:
   a) Two or more ACUTE pain crises in a 12-month period requiring emergency room/medical facility treatment with a parenterally administered opioid or parenterally administered ketorolac
   OR
   b) Recurrent acute chest syndrome

AND

4. (a) Documentation member has had an inadequate response to an adherent, maximally tolerated dose of Hydroxyurea for the past 180 days
   OR
   (b) Documentation member has serious side effects or contraindication to the use of Hydroxyurea

CONTINUATION OF THERAPY:

A. SICKLE CELL DISEASE:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Documentation member has had a reduction in the number of crisis and/or acute chest syndrome episodes since initiating therapy.
   AND
3. Member continues on an FDA approved dose.
   AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a hematologist or a physician who specializes in sickle cell disease [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

5 years of age and older

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

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Amino Acid

FDA-APPROVED USES:
Indicated to 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

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Sickle cell disease (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, 1in 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]

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Endari (L-glutamine) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Endari (L-glutamine) include: No labeled contraindications.

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.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Endari PACK 5GM
L-Glutamine PACK 5 GM

REFERENCES

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4. 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
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION-Notable Revisions: References	Q2 2025
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2024
REVISION-Notable Revisions: Required Medical Information Continuation of Therapy Duration of Approval Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q2 2023
REVISION-Notable Revisions Prescriber Requirements	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file