Endari

I. Generic Name:

a. L-Glutamine

II. Brand Name:

a. Endari

III. Medication Class:

a. Amino acid: glutamine serves as a precursor to nicotinamide adenine dinucleotide (NAD); the NADH to NAD ratio is lowered in sickle red blood cells and contributes to increased oxidative stress; glutamine addition may improve NAD redox potential in sickle red blood cells through increased availability of reduced glutathione

IV. FDA Approved Uses:

a. Sickle cell disease (SCD): Prevention of vaso-occlusive pain episodes in patients with frequent episodes (greater than or equal to 2 in the past 12 months) for patients age 5 years and older

V. Application of Criteria:

a. The following criteria apply to Illinois Medicaid and Meridian Choice (HIX)
b. Please refer to Michigan Medicaid Managed Care Organization Common Criteria for requests for Michigan Medicaid members

VI. Criteria for Use:

a. Member must be 5 years of age or older
b. Prescribed by a hematologist/oncologist
c. Current chart notes with plan of care recommending treatment with Endari
d. Clear documentation of severity and frequency of vaso-occlusive pain crises (VOCs)
e. Documentation that the patient has had 2 or more episodes of VOCs within the past 12 months
f. Documentation of adequate trial and failure and compliance to appropriate maximum tolerated dose of Hydroxyurea
g. Current CBC, current renal function and current hepatic function lab/test results
h. Related lab work/test results such as neonatal genetic screening, high-performance liquid chromatography (HPLC), iso-electric focusing (IEF), direct DNA testing, or gel electrophoresis, supporting the diagnosis of one of the following genotypes:

A. (Refer to Table 1): Please note that hemoglobin electrophoresis testing after transfusion of red cells can result in an incorrect diagnosis. In such cases, sickle cell diagnosis should utilize DNA testing or be postponed for at least four months after transfusion.
B. Homozygous sickle cell (HbSS) disease
C. Sickle-cell Beta+ thalassemia (SC-Beta+)
D. Sickle-cell Beta0 thalassemia (SC-Beta0)
E. Hemoglobin SC (HbSc) disease

VII. Required Medical Information:

a. Proper diagnosis and documentation of an FDA approved indication
b. Current progress notes detailing the diagnosis with plan of care
c. Documentation of dose, date ranges of therapy, and clinical outcomes for all medications previously tried and failed
d. Complete chart notes documenting disease history
e. Related lab work/test results
f. Charts showing compliance to previous therapy and office visits

VIII. Contraindications:

a. Hypersensitivity to Endari or any component of the formulation

IX. Not Approved If:

a. Request is for Endari (L-Glutamine) as combination therapy used concurrently with either Oxbryta (voxelotor) or Adakveo (crizanlizumab)
b. Patient shows non-compliance with previous treatment based on progress notes and/or pharmacy claims/fill history for required step therapies
c. Patient shows any contraindications to the use of Endari as outlined in the FDA approved prescribing information
d. Request is for a non-FDA approved indication or dose

X. Length of Authorization:

a. Initial: 3 months
b. Continuation: up to 6 months

XI. Dosing:

a. Weight < 30kg
    A. 5g (1 packet) twice daily (total dose 10g/day)
b. Weight 30kg to 65kg
    A. 10g (2 packets) twice daily (total dose 20g/day)
c. Weight > 65kg
    A. 15g (3 packets) twice daily (total dose 30g/day)

XII. Criteria for Continuation of Therapy:

a. Initial therapy was tolerated
b. Demonstrated improvement in disease (reduction in the number of VOCs)
c. Patient must be compliant with taking the medication as prescribed
d. Patient must not be experiencing any severe adverse reaction while taking the medication
e. Office visit every 3-6 months with verified compliance and improvement or stability on drug

XII. Criteria for Discontinuation of Therapy:

a. Patient is non-compliant with pharmacologic or non-pharmacologic therapy
b. No demonstrable clinically significant improvement after initiation and stabilization of drug therapy
c. Patient is non-responsive to FDA-approved usual maximum dosing

XIII. References:

1. L-glutamine: Facts and Comparisons. Wolters Kluwer Health. December 2019
2. Endari (L-glutamine oral powder) Prescribing Information. Torrance, CA; Emmaus Medical, Inc.: July 2017.
3. Yawn BP, Buchanan GR, Afenyi-annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014; 312(10):1033-48.
4. Ryan K, Bain BJ, Worthington D, et al. Significant haemoglobinopathies: guidelines for screening and diagnosis. Br J Haematol. 2010; 149(1):35-49.
5. Torres L, Conran N. Emerging pharmacotherapeutic approaches for the management of sickle cell disease. Expert Opin Pharmacother. 2019; 20(2):173-186.
6. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018; 379 (3):226-235.

Table 1. Hemoglobin patterns in common hemoglobinopathies

				Older children (>5 years, adolescents, and adults)				
Phenotype	**Genotype**	Neonatal Screen	Age = 6 weeks screening	**HbA (%)**	**HbA2 (%)**	**HbF (%)**	**HbS (%)**	**HbC (%)**
Normal	AA	FA	FA or AF	95 – 98	2 – 3	< 2	0	0
HbSS disease	**SS**	**FS**	**FS**	**0**	**< 3.5**	**5 - 15 (or higher)**	**85 – 95**	**0**
SC-Beta+	**SBeta+**	**FSA or FS**	**FSA**	**3 – 30**	**> 3.5**	**2- 10**	**65 – 90**	**0**
SC-Beta0	**SBeta0**	**FS**	**FS**	**0**	**> 3.5**	**2 - 15**	**80 – 92**	**0**
HbSc disease	**SC**	**FSC**	**FSC**	**0**	**< 3.5**	**1 – 5 (or higher)**	**45 – 50**	**45 – 50**
Beta thalassemia trait	A/(Beta or Beta+)	FA	FA	90 – 95	> 3.5	1 – 3	0	0
Sickle cell trait	AS	FAS	FAS	50 – 60	< 3.5	< 2	35 – 45 (lower if concomitant alpha thalassemia)	0

Endari

Approved by: _____ Date: _____

CMO

Initial Approval:	
Revised:	
Annual Review:	
Next Review Date:	