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Endari (L-glutamine) Prior Authorization Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Endari™ (L-glutamine) Oral powder	To reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	Orally twice daily

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

CLINICAL RATIONALE

Sickle cell disease (SCD) is the name given to a group of lifelong inherited conditions that affect hemoglobin. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent shape.[2]

Signs and symptoms of SCD usually begin in early childhood. Characteristic features of SCD include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person and can range from mild to requiring frequent hospitalizations.[2]

SCD effects nearly every system in the body. SCD has both acute and chronic complications. An episode of severe pain [acute vaso-occlusive crisis (VOC)] is the most common acute complication of SCD. In addition to VOCs other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Chronic complications of SCD can affect almost any organ, and certain acute complications often evolve into chronic phases. The most common chronic complications of SCD include chronic pain, chronic anemia, avascular necrosis, leg ulcers, pulmonary hypertension, renal complications, stuttering/recurrent priapism, and ophthalmologic complications.[2]

Pain is the most common complication of SCD for both acute and chronic complications. Pain can be acute, chronic, or an acute episode superimposed on chronic pain. In SCD, pain is considered chronic if it lasts more than 3 months. People with SCD experience both nociceptive and neuropathic pain.[2]

Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease. Discoveries over the past 2 decades have highlighted the important contributions of various cellular and soluble participants in the vaso-occlusive cascade. Although the molecular basis of SCD is well characterized, the complex mechanisms underlying VOC have not been fully elucidated. Based on direct observations in SCD mice, adhesive interactions of SS-RBCs and leukocytes to the endothelium play important roles in the initiation of VOC. It is thought that the activated adherent leukocytes, which are rigid and larger than sickle cell-red

blood cells (SS-RBC), likely drive VOC in collecting venules, whereas the SS-RBCs may contribute in smaller vessels or in situations where there is no potent inflammatory trigger.[4]

Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, hemolysis, or a combination of the following factors:[4]

- Endothelial activation by SS-RBCs and other inflammatory mediators
- Recruitment of adherent leukocytes
- Activation of recruited neutrophils and of other leukocytes (e.g., monocytes or iNKT cells)
- Interactions of sickle erythrocytes with adherent neutrophils
- Vascular clogging by heterotypic cell-cell aggregates composed of SS-RBCs, adherent leukocytes and possibly platelets
- Increased transit time to greater than the delay time for deoxygenation-induced hemoglobin polymerization, propagating retrograde VOC
- Ischemia as a result of the obstruction that creates a feedback loop of worsening endothelial activation

Sickle hemoglobin can cause damage to the RBC membrane from deformation by polymer formation. In addition, the mutated globin can undergo autooxidation and precipitate on the inner surface of the RBC membrane, causing membrane damage via iron-mediated generation of oxidants. Both endothelial selectins, P-selectin and E-selectin, have been suggested to participate in VOC.[4]

Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ^+-thalassemia, HbSβ^0-thalassemia). It is important for the patient and the primary care provider to know the baseline or "steady state" hemoglobin value to inform ongoing monitoring and management during acute complications.[2]

Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as an option to increase HbF levels in people with SCD. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia (SCA) involved two people. The results of this study showed favorable outcomes which lead to two extended studies with larger cohorts of people. Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of actions and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises RBC volume [higher mean corpuscular volume (MCV)] and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion.[3]

An expert panel report of evidence-based management of sickle cell disease supports the use of hydroxyurea with strong recommendations in the following:[3]

- In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12 month period
- In adults with SCA who have sickle cell-associated pain that interferes with daily activity and quality of life
- In adults with SCA who have a history of severe and/or recurrent acute coronary syndrome (ACS)
- In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
- In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia)

A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, the expert panel report of evidence-based management of sickle cell disease recommends a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.[3]

Efficacy[1]
The mechanism of action of the amino acid L-glutamine in treating sickle cell disease (SCD) is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, NAD+ and its reduced form NADH, play roles in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.

The efficacy of L-glutamine was evaluated in a randomized, double-blind, placebo controlled, multi-center clinical trial with 230 patients. Efficacy was demonstrated by a reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering among patients that received L-glutamine compared to patients who received placebo. The recurrent crisis event time analysis yielded an intensity rate ratio (IRR) value of 0.75 with 95% CI= (0.62, 0.90) and (0.55, 1.01) based on unstratified models using the Andersen-Gill and Lin, Wei, Yang and Ying methods, respectively in favor of L-glutamine, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 25% from the L-glutamine group over the placebo group.

Safety[1]
Endari (L-glutamine) has no FDA labeled contraindications.

REFERENCES

1. Endari prescribing information. Emmaus Medical, Inc. October 2020.
2. U.S. National Library of Medicine. Genetics Home Reference. Sickle cell disease. November 2019.
3. U.S. Department of Health and Human Services. National Institute of Health. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014.
4. Manwani D, Frenette PS, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood. 2013 Dec 5; 122(24): 3892-3898.

Endari (L-glutamine) Prior Authorization

TARGET AGENT(S)
Endari™ (L-glutamine)

Brand (generic)	GPI	Multisource Code
Endari (L-glutamine)		
5 g packet	82801020003020	M, N, O, or Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of sickle cell disease
   AND
2. The patient is using the requested agent to reduce the acute complications of sickle cell disease
   AND
3. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent
      OR
   B. The prescriber has provided information in support of using the requested agent for the patient's age
   AND
4. ONE of the following
   A. The patient has tried and had an inadequate response to maximally tolerated hydroxyurea used for at least 6 months
      OR
   B. The patient has an intolerance or hypersensitivity to hydroxyurea
      OR
   C. The patient has an FDA labeled contraindication to hydroxyurea
   AND
5. ONE of the following:
   A. The patient will not be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor)
      OR
   B. Information has been provided supporting the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Oxbryta (voxelotor)
   AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
7. The requested quantity (dose) does not exceed the maximum FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved through the plan's Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent (i.e., reduction in acute complications of sickle cell disease since initiating therapy with the requested agent)

AND

3. ONE of the following:
    A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor)
    OR
    B. Information has been provided supporting the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Oxbryta (voxelotor)

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months