Endari™ Prior Authorization Program Summary

This prior authorization applies to Commercial, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the Endari Prior Authorization is to encourage appropriate selection of patients for treatment and dosing according to product labeling, and/or clinical studies, and/or guidelines. The program will not allow approval for patients who have an FDA labeled contraindication to the requested agent. Requests will be reviewed when patient specific documentation is provided.

TARGET AGENT
Endari™ (L-glutamine)

Prior Authorization Target

Agent	GPI	MultiSource Code
Endari (L-glutamine) 5 g packet	82801020003020	M, N, O, Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Endari 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. The patient is 5 years of age or greater
   AND
4. ONE of the following
   a. The patient has tried and received inadequate response to therapy with hydroxyurea therapy
      OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to hydroxyurea
   AND
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
6. ONE of the following:
   a. The requested dose is within the FDA labeled dose
      OR
   b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Initial Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved through the Prime Therapeutics prior authorization process for the requested agent
   AND
2. The prescriber has indicated that the patient has seen a reduction in acute complications of sickle cell disease since initiating therapy with Endari
   AND
3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
4. ONE of the following:
   a. The requested dose is within the FDA labeled dose
      OR
   b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Renewal Approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1]

<table>
<tr><th>Agent</th><th>Indication</th><th>Dosage & Administration</th></tr>
<tr><td>Endari™ (L-glutamine)</td><td>To reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older</td><td>
<table>
<tr><td>Weight in Pounds</td><td>Per dose in grams</td><td>Per day in grams</td><td>Packets per dose</td><td>Packets per day</td></tr>
<tr><td>Less than 66</td><td>5</td><td>10</td><td>1</td><td>2</td></tr>
<tr><td>66-143</td><td>10</td><td>20</td><td>2</td><td>4</td></tr>
<tr><td>Greater than 143</td><td>15</td><td>30</td><td>3</td><td>6</td></tr>
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CLINICAL RATIONALE

Guidelines

Hydroxyurea is a mainstay in the management of sickle cell disease. It reduces the incidence of acute painful episodes and hospitalization rates, and prolongs survival.[2,3]

Efficacy[1]

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]

L-glutamine carries no black box warnings or contraindications.

REFERENCES

1. Endari prescribing information. Emmaus Medical, Inc. July 2017.
2. Overview of the management and prognosis of sickle cell disease. UpToDate. Literature review current through 10/2017. Last updated 10/23/2017. Accessed 11/30/2017
3. Evidence-based management of sickle cell disease; expert panel report 2014. National Heart, Lung, Blood Institute. Available at https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines