

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENDARI™ safely and effectively. See full prescribing information for ENDARI.

ENDARI (L-glutamine oral powder)
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ENDARI 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. (1)

DOSAGE AND ADMINISTRATION

- 5 grams to 15 grams orally, twice daily based on body weight. (2)
- Each dose of Endari should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before ingestion. (2)

DOSAGE FORMS AND STRENGTHS

Oral Powder: 5 grams of L-glutamine powder per paper-foil-plastic laminate packet. (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 10%) are constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Emmaus Medical, Inc. at 1-877-420-6493 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

2.2 Preparation of Product

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Clinical Studies

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Endari is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Administer Endari orally, twice per day at the dose based on body weight according to Table 1.

Table 1. Recommended Dosing

Weight in kilograms	Weight in pounds	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

2.2 Preparation of Product

Mix Endari immediately before ingestion with 8 oz. (240 mL) of cold or room temperature beverage, such as water, milk or apple juice, or 4 oz. to 6 oz. of food such as applesauce or yogurt. Complete dissolution is not required prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Oral powder: 5 grams of L–glutamine as a white crystalline powder in paper-foil-plastic laminate packets

4 CONTRAINDICATIONS

None

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Endari in 187 patients, including 136 exposed for 6 months and 109 exposed for ≥ 1 year. Endari was studied in 2 placebo-controlled clinical trials (a phase 3 study, n=230 and a phase 2 study, n=70). In these trials, patients with sickle cell anemia or sickle β^0 -thalassemia were randomized to receive Endari (n=187) or placebo (n=111) orally twice daily for 48 weeks followed by 3 weeks of tapering. Both studies included pediatric and adult patients (5-58 years of age) and 54% were female. The majority of patients were black (97.3%), had a diagnosis of sickle cell anemia (89.9%) and were receiving hydroxyurea at baseline (63.4%).

Treatment discontinuation due to adverse reactions was reported in 2.7% (n=5) of patients receiving Endari. These adverse reactions included one case each of hypersplenism, abdominal pain, dyspepsia, burning sensation, and hot flash.

Serious adverse reactions were reported in both treatment groups, more frequently in the placebo group, and were consistent with the underlying disease.

Three deaths (3/187=1.6%) occurred during the study in the Endari treatment group as compared to none in the placebo treatment group. None of the deaths were considered to be related to Endari treatment. Adverse reactions occurring in greater than 10% of patients treated with Endari are shown in [Table 2](#) below.

Table 2. Adverse Reactions Occurring at an Incidence > 10% in Clinical Studies of Endari

Adverse reaction	Endari N = 187 (%)	Placebo N = 111 (%)
Constipation	21	18
Nausea	19	14
Headache	18	15
Abdominal Pain ¹	17	16
Cough	16	14
Pain in extremity	13	7
Back pain	12	5
Chest pain	12	8

¹Abdominal pain = abdominal pain and abdominal pain, upper

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Endari use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies were not conducted with Endari.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of Endari in human milk, the effect on the breastfed infant or the effect on milk production. The developmental and health benefits from breastfeeding should be considered along with the mother's clinical need for Endari and any potential adverse effects on the breastfed child from Endari or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Endari have been established in pediatric patients 5 years and older. Use of Endari is supported by evidence from 2 placebo-controlled studies in adult and pediatric patients with sickle cell disease. The clinical studies enrolled 110 pediatric patients in the following age groups: 46 children (5 years up to less than 12 years) and 64 adolescents (12 years to less than 17 years).

The safety and effectiveness of Endari in pediatric patients with sickle cell disease younger than 5 years old has not been established.

8.5 Geriatric Use

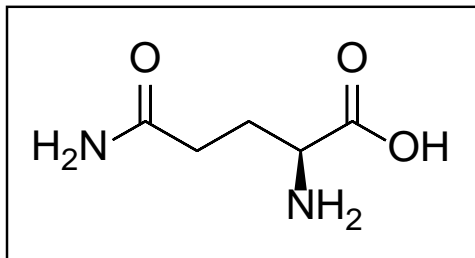
Clinical studies of Endari did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Single oral doses of L-glutamine at about 20 g/kg to 22 g/kg, 8 g/kg to 11 g/kg, and 19 g/kg were lethal in mice, rats, and rabbits, respectively. Supportive measures should be undertaken in the event of overdose of Endari.

11 DESCRIPTION

Endari (L-glutamine) is an amino acid. L-glutamine is designated chemically as (S)-2-aminoglutaramic acid, L-glutamic acid 5-amide, or (S)-2,5-diamino-5-oxopentanoic acid. The molecular formula is $C_5H_{10}N_2O_3$ with the molecular weight of 146.15 g/mol and the following structural formula:



Endari is formulated as a white crystalline powder and is packaged as 5 grams in a paper-foil-plastic laminate packet for oral administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

In vivo analyses demonstrated that L-glutamine supplementation improved NAD redox potential.

12.3 Pharmacokinetics

The pharmacokinetics of L-glutamine has been studied in healthy subjects and a variety of disease states. Relevant results from published literature are summarized below.

Absorption

Following single-dose oral administration of L-glutamine at 0.1 g/kg, mean peak L-glutamine concentration was 1028 μ M (or 150 mcg/mL) occurring approximately 30 minutes after administration. The pharmacokinetics following multiple oral doses has not been characterized.

Distribution

After an intravenous (IV) bolus dose, the volume of distribution was estimated to be approximately 200 mL/kg.

Elimination

After an intravenous bolus dose, the terminal half-life of L-glutamine was approximately one hour.

Metabolism

Endogenous L-glutamine participates in various metabolic activities, including the formation of glutamate, and synthesis of proteins, nucleotides, and amino sugars. Exogenous L-glutamine is anticipated to undergo similar metabolism.

Excretion

Metabolism is the major route of elimination for L-glutamine. Although L-glutamine is eliminated by glomerular filtration, it is almost completely reabsorbed by the renal tubules.

Specific Populations

The safety of Endari has not been established in patients with renal or hepatic impairment.

Drug Interactions

No drug interaction studies have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of L-glutamine.

L-glutamine was not mutagenic in a bacterial mutagenicity (Ames) assay, nor clastogenic in a chromosome aberration assay in mammalian (Chinese Hamster Lung CHL/IU) cells.

Animal reproduction studies and its potential for impairment of fertility have not been conducted with L-glutamine. It is also not known whether L-glutamine can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

14 Clinical Studies

The efficacy of Endari in sickle cell disease was evaluated in a randomized, double-blind, placebo-controlled, multi-center clinical trial entitled “A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle β^0 -thalassemia” [NCT01179217] (see [Table 3](#)).

The clinical trial evaluated the efficacy and safety of Endari in 230 patients (5 to 58 years of age) with sickle cell anemia or sickle β^0 -thalassemia who had 2 or more painful crises within 12 months prior to enrollment. Eligible patients stabilized on hydroxyurea for at least 3 months continued their therapy throughout the study. The trial excluded patients who had received blood products within 3 weeks, had renal insufficiency or uncontrolled liver disease, or were pregnant (or planning pregnancy) or lactating. Study patients received Endari or placebo for a treatment duration of 48 weeks followed by 3 weeks of tapering.

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 Endari compared to patients who received placebo. A sickle cell crisis was defined as a visit to an emergency room/medical facility for sickle cell disease-related pain which was treated with a parenterally administered narcotic or parenterally administered ketorolac. In addition, the occurrence of chest syndrome, priapism, and splenic

sequestration were considered sickle cell crises. Treatment with Endari also resulted in fewer hospitalizations due to sickle cell pain at Week 48, fewer cumulative days in hospital and a lower incidence of acute chest syndrome.

Table 3. Results from the Endari Clinical Trial in Sickle Cell Disease

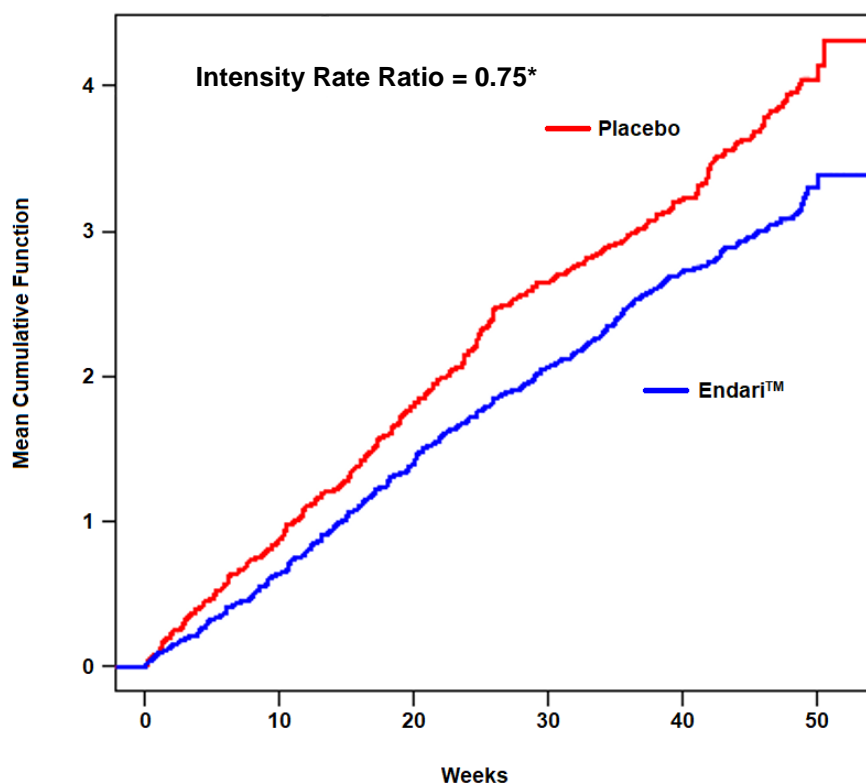
Event	Endari (n = 152)	Placebo (n = 78)
Median number of sickle cell crises (min,max) ¹	3 (0, 15)	4 (0, 15)
Median number of hospitalizations for sickle cell pain (min, max) ¹	2 (0, 14)	3 (0, 13)
Median cumulative days in hospital (min, max) ¹ ,	6.5 (0, 94)	11 (0, 187)
Median time (days) to first sickle cell crisis (95% CI) ^{1,2}	84 (62, 109)	54 (31, 73)
Patients with occurrences of acute chest syndrome (%) ¹	13 (8.6%)	18 (23.1%)

¹ Measured through 48 weeks of treatment

² Hazard Ratio=0.69 (95% CI=0.52, 0.93), estimated based on unstratified Cox's proportional model. Median time and 95% CI were estimated based on the Kaplan Meier method.

The recurrent crisis event time analysis (Figure 1) 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 Endari, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 25% from the Endari group over the placebo group.

Figure 1. Recurrent Event Time for Sickle Cell Crises by Treatment Group



*Anderson-Gill: 95% CI (0.62, 0.90); Lin-Wei-Yang-Ying: 95% CI (0.55, 1.01)

16 HOW SUPPLIED/STORAGE AND HANDLING

Endari is supplied in paper-foil-plastic laminate packets containing 5 grams of L-glutamine white crystalline powder.

- Carton of 60 packets: NDC 42457-420-60

Store at 20°C to 25°C (68°F to 77°F) away from direct sunlight.

17 PATIENT COUNSELING INFORMATION

Dosage and Administration

Advise patient to take a missed dose as soon as they remember. Patient should not double the dose that they take.

Instruct patient to mix each dose in 8 oz. (240 mL) of cold or room temperature beverage or 4 to 6 oz. of food.

Advise patient that complete dissolution is not required prior to administration.

Manufactured for:
Emmaus Medical, Inc
Torrance, CA 90503

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
07/07/2017