

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208587Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Ann. T. Farrell, M.D., Division Director
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	208587 505(b) (2)
<b>Supplement #</b>	
<b>Applicant Name</b>	Emmaus Medical Inc.
<b>Date of Submission</b>	09/07/16
<b>PDUFA Goal Date</b>	07/07/17
<b>Proprietary Name / Non-proprietary Name</b>	Endari/L-glutamine powder
<b>Dosage Forms / Strength</b>	5 gram paper-foil-plastic laminate packets
<b>Proposed Indication(s)</b>	for the treatment of sickle cell disease
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Regulatory Health Project Manager	
Associate Director for Labeling	Virginia Kwitkowski, RN, MS, AC-BP
Medical Officer Review	Rosanna Setse, M.D, Ph.D./Kathy Robie-Suh, M.D., PhD.
Statistical Review	Che Smith, Ph.D./Yuan-Li Shen, Dr. PH./Thomas Gwise, Ph.D.
Pharmacology Toxicology Review	Luan Lee, Ph.D./Christopher Sheth, Ph.D.
CMC Review/OBP Review	Rajan Pragani/Zhaoyang Meng/Ephrem Hunde/Rabiya Laiq/Katherine Jacobitz/
Microbiology Review	See above
Clinical Pharmacology Review	Yuhong Chen, M.D., Ph.D./Stacy Shord, Pharm.D./NAM Atiqur Rahman, Ph.D.
OPDP/DDMAC	Rachel Conklin/Kathleen Davis/ Idalia E. Rychlik/Hina Mehta/Leeza Rahimi
OSI	Min Lu, M.D, M.P.H./ Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Reviews	Kathy Robie-Suh, M.D., PhD.

## Signatory Authority Review Template

### 1. Introduction

Emmaus Medical Inc submitted a new drug application (505 (b) (2) NDA) for L-glutamine for the treatment of sickle cell disease. Emmaus has previously been granted approval for L-glutamine (NDA 21667) marketed as NutreStore for the treatment of short bowel syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication on June 10, 2004. The PDUFA goal date is July 7, 2017.

L-glutamine is a naturally occurring amino acid.

### 2. Background

Only hydroxyurea (Droxia) is approved for the treatment of sickle cell disease. While hydroxyurea is effective, not all patients respond and thus this disease area has a need for more effective therapies. Hematopoietic stem cell transplantation offers potential cure; however few patients are eligible for this treatment option.

This application contains data from Study GLUSCC09-01 and Study 10478 were multicenter, double-blind, randomized, placebo-controlled trials designed to evaluate the long-term efficacy and safety of Endari for the treatment of sickle cell disease in patients with sickle cell anemia and sickle  $\beta^0$ -thalassemia who were at least 5 years of age. The primary efficacy endpoint for both trials was the number of sickle cell crises at Week 48.

### 3. CMC/Device

No issues which would preclude approval were identified. From the review:

*As part of this action, OPQ grants a <sup>(b) (4)</sup> month re-test period for the drug substance for storage at <sup>(b) (4)</sup>. OPQ grants a 48 month drug product expiration period for storage at 25°C <sup>(b) (4)</sup> in the commercial packaging.*

### 4. Nonclinical Pharmacology/Toxicology

No issues which would preclude approval were identified. The review team agreed with the proposal to waive the requirement for a carcinogenicity study.

### 5. Clinical Pharmacology/Biopharmaceutics

The following is from the Office of Clinical Pharmacology review:

*In an open-label, single-center, sequential study (Study 8288) in 11 adults with SCD, the ratio of NADH to total NAD levels increased from 47% to 62% following a dose of 30 grams per day for 4 weeks; no changes were observed following lower doses.*

There were no issues regarding approval. However the team recommended the following due to a subgroup analysis in patients with lower body weight which suggested a reduced benefit compared to those weighing more than 65 kg:

*A post-marketing commitment (PMC) will be issued to recommend that the Applicant conduct a 24-week clinical trial in adult and pediatric patients to identify a dose in patients with body weight  $\leq$  65 kg that similarly increases the ratio of NADH to total NAD levels from the baseline as compared to a dose of 30 grams per day in patients with body weight  $>$  65 kg, and that demonstrates comparative efficacy and safety to a dose of 30 grams per day in patients with body weight  $>$  65 kg. The study population should reflect the typical population of patients with SCD in the United States, especially regarding organ function.*

## **6. Clinical Microbiology**

N/A

## **7. Clinical/Statistical-Efficacy**

The clinical review team reviewed the two submitted clinical studies.

From the primary clinical review:

*This reviewer recommends regular approval of Endari for the indication of “the treatment of sickle cell disease”. Approval is based on the observed estimated mean cumulative rates of sickle cell crises of 3 versus 3.8 for Endari versus placebo treated patients respectively at Week 48 [Hazard ratio (HR) 0.73, 95% CI: (0.55, 0.99)]. This conclusion is supported by the comparable safety profile (serious adverse events (SAEs), SAEs related to study treatment, treatment emergent adverse events (TEAEs) and TEAEs that led to study drug withdrawal) of Endari in patients with sickle cell disease (SCD) compared to placebo; and the lower frequency of occurrence of disease related SAEs [sickle cell anemia with crisis and acute chest syndrome (ACS)] in patients with SCD treated with Endari versus placebo.*

*Based on the data in this submission, this reviewer agrees with the clinical pharmacology recommendation that a PMC should be issued to the Applicant to conduct an additional study post-approval to optimize the dose of Endari in patients with body weights of 65 kilograms or less.*

The review team was concerned with the amount of missing data and the imputation methods the Applicant used to overcome the impact of the missing efficacy data.

Nearly all the sensitivity analyses and imputations methods the review team used led to the same conclusion that the analyses suggested a benefit for using L-glutamine.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy.

## **8. Safety**

The most commonly reported adverse events were constipation, nausea, headache, pyrexia, abdominal pain, and cough.

The deaths that occurred in patients treated with L-glutamine were not considered treatment-related.

## **9. Advisory Committee Meeting**

This product was discussed at an Oncologic Drugs Advisory Committee meeting on May 24, 2017. The Agency brought the following issues to the AC meeting: the missing efficacy data and the imputation methods used due to the missing data by the Applicant. The committee voted 10 to 3 that the applicant had demonstrated that L-glutamine had a favorable risk benefit.

## **10. Pediatrics**

Pediatric patients were enrolled in the clinical trials that were used for the approval decision.

## **11. Other Relevant Regulatory Issues**

### Office of Scientific Investigation (OSI)

Data collected were deemed reliable in support of the application.

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

The labeling was reviewed by all disciplines and consultant staff.

## **13. Decision/Action/Risk Benefit Assessment**

- Recommended regulatory action

Approval

- Risk Benefit Assessment

Despite the concerns regarding methods of imputation and the impact on the primary analysis, almost all analyses suggested that L-glutamine treatment is associated with fewer acute complications of sickle cell disease at Week 48 compared to placebo treatment. The most commonly reported adverse events in patients treated with L-glutamine were constipation, nausea, headache,

pyrexia, abdominal pain, and cough. The risk-benefit appears favorable. Due to an exploratory analysis which suggested a reduced benefit with L-glutamine treatment in patients less than 65 kg, a PMC was negotiated (see below).

- Recommendation for Post marketing Risk Management Activities (PMR) – Routine post market surveillance plus PMR under FDAAA
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

We have asked the applicant for the following PMC (draft not final language):

To design and conduct a dose finding trial in adult and pediatric patients with body weight lower or equal to 65 kg. The primary endpoint will be an increase in the ratio of NADH to total NAD levels from the baseline. The study design will include a comparison to the increase in the ratio of NADH to total NDA levels at baseline for patients with body weight higher than 65 kg administered a dose of 30 grams per day. The trial will include analyses of safety and activity of the doses. The study population should include patients with renal and hepatic impairment.

For final versions of the PMRs and PMC see the approval letter.

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/s/  
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ANN T FARRELL  
06/27/2017