CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208587
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Submission Date	09/07/2016
Submission Type	Standard review
Brand Name	Endari
Generic Name	L-glutamine
Dosage Form and Strength	Paper-foil-plastic laminate packets containing 5 grams (g) of L-glutamine powder
Route of Administration	Oral
Proposed Indication	For the treatment of sickle cell disease (SCD)
Applicant	Emmaus Medical Inc
Associated Applications	IND 053841 NDA 21667
OCP Review Team	Yuhong Chen, MD & Ph.D. Stacy S. Shord, Pharm.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. Director, Division of Clinical Pharmacology V

Table of Contents

1. EXECUTIVE SUMMARY

L-glutamine oral powder as NutreStore was approved for the treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone in June 2004. The Applicant submitted the current application to support the use of L-glutamine oral powder for the treatment of patients with Sickle Cell Disease (SCD). L-glutamine is an amino acid found in the human body that is a precursor of glutathione, nucleic acids and pyridine nucleotides. The proposed total daily dose is 10 grams, 20 grams, or 30 grams divided into two doses; the dose selected is based on actual body weight. The efficacy and safety was supported by a randomized, placebo controlled phase III trial with additional efficacy and safety data provided from a smaller, randomized phase II trial. L-glutamine oral powder reduced the mean frequency of crises compared to placebo in the total population [L-glutamine 3 vs. placebo 3.8 crises in 48 weeks; relative risk: 0.73 (95% confidence interval (CI): 0.55, 0.99)]. A subgroup analysis suggested patients with body weight ≤ 65 kg and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day may not benefit from L-glutamine compared to placebo [L-glutamine 2 vs. placebo 2.5 crises in 48 weeks; relative risk: 0.87 (95% CI: 0.63, 1.19)]. Pediatric patients were included in this subgroup analysis and may show poorer response. The most common adverse reactions, sickle cell anemia with crisis and acute chest syndrome, occurred less frequently in patients administered L-glutamine oral powder vs. placebo.

No dedicated clinical pharmacology studies were conducted. The Applicant relied on publicly available data from published literature and the Nutrestore labeling to describe the clinical pharmacology. The Application is approvable from clinical pharmacology perspective as the totality of the efficacy and safety data showed L-glutamine provides benefit to the patients with SCD who have limited treatment options; hydroxyurea is the only approved drug for the treatment of SCD in the US.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of the NDA 208587 from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The results of the randomized phase III trial demonstrated fewer sickle cell crises in favor of L-glutamine oral powder relative to placebo in the total population. The results of the phase II trial similarly showed that the median number of crises in the patients administered L-glutamine oral powder was lower compared to patients administered placebo. Pharmacokinetic (PK) and pharmacodynamic (PD) samples were not collected during these trials.
General dosing instructions	The proposed total daily dose based on actual body weight is as follows: 10 grams (less than 30 kg), 20 grams (30 kg to 65 kg), or 30 grams (greater than 65 kg). The oral powder is to be mixed with cold or room temperature beverage or food. The effect of temperature or food on the bioavailability of L-glutamine was not evaluated.

Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization is recommended based on actual body weight. The effects of organ impairment or other factors were not evaluated. A trial to determine an appropriate dose for patients with body weight ≤ 65 kg will be recommended based on subgroup analysis that suggests less benefit for patients who received a dose of 10 grams or 20 grams, including patients ≤ 18 years.
Labeling	Generally acceptable. The review team made recommendations for specific content and formatting changes.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed drug product was administered in the phase III and phase II trials.

1.2 Post-Marketing Requirements and Commitments

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 ≤ 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.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: The mechanism of action of L-glutamine in SCD is not fully understood. The Applicant proposes that L-glutamine may improve the NAD redox potential in sickle red blood cells (RBC) by increasing the availability of reduced glutathione. The subsequent effects of L-glutamine on redox potential in sickle RBC may improve clinical response.

Pharmacokinetics: As described in the published literature and the Nutrestore labeling.

Absorption

Following a single oral dose of 0.1 g/kg (~8.5 g), mean peak L-glutamine concentration of 1028 µM (or 150 µg/mL) occurred approximately 30 minutes after administration.

Enteral glutamine administration increased plasma glutamine levels in a dose- dependent manner to levels as high as 2773 µmol/L (following administration of 126 mmol/h enteral glutamine). An oral glutamine dose of 0.3 g/kg (equivalent of 18 g to 32 g) resulted in a peak plasma concentration of 1328 ± 99 µmol/L at 45 minutes after dosing.

The PK following multiple oral doses has not been characterized. The effect of food on L-glutamine has not been evaluated.

Distribution

After an intravenous bolus, the volume of distribution is estimated to be ~ 200 mL/kg.

Elimination

After an intravenous bolus, the terminal half-life is ~ 1 hour.

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

L-glutamine is eliminated by glomerular filtration, but it is reabsorbed by the renal tubules.

Drug Interactions

No drug interaction studies have been conducted.

Specific Populations

The PK of L-glutamine was evaluated in 13 patients 3 years to 18 years of age with a hematologic or solid tumor malignancy. A single oral (or nasogastric tube in 2 patients) dose was administered as follows: 0.35 g/kg to 3 patients, 0.5 g/kg in 6 patients, 0.65 g/kg in 3 patients. The mean time to the maximum concentration (T_{max}) ranged from 40 minutes to 80 minutes and the mean area under the curve (AUC) increased in a less than dose-proportional manner.

The effect of body weight, organ impairment or other intrinsic factors on the PK or PD has not been evaluated.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is a total daily dose of 0.3 g/kg per day divided into two doses. The dose should be mixed with cold or room temperature beverage or food immediately before ingestion. The Applicant proposed a weight based total daily dose of 10 grams for patients weighing less than 30 kg, 20 grams for patients weighing 30 kg to 65 kg and 30 grams for patients weighing greater than 65 kg. The effect of food on PK or PD has not been evaluated.

The dose selection was based on the changes in the ratio of NADH to total NAD levels from the baseline in 11 adults with sickle cell disease (Study 8288). Of note, the recommended dose for patients with SBS is 30 grams (or 0.3 g/kg) per day mixed in (b) (4) mL of water (b) (4) (b) (4)

2.2.2 Therapeutic individualization

Dose individualization is based on actual body weight. The effects of body weight or other intrinsic factors on the PK or PD have not been evaluated.

2.3 Outstanding Issues

The available data suggest that L-glutamine does not provide similar benefit in patients weighing ≤ 65 kg compared to patients weighting > 65 kg. Patients weighing ≤ 65 kg received a total daily dose of 10 grams or 20 grams. The following data suggests that these dose levels may not provide clinically meaningful benefit.

- These dose levels did not increase the ratio of NADH to total NAD levels from the baseline in adult patients based on the results of the dose finding study (Study 8288), and the increase in the ratio of NADH to total NAD levels from baseline is the foundation of the Applicant's hypothesis that L-glutamine maybe a promising treatment for SCD.

- The Applicant did not provide justification for a weight based dose as compared to the flat dose used in the dose finding study.
- The efficacy data from the phase III trial suggests that patients with body weight ≤ 65 kg and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day may not benefit from L-glutamine compared to placebo [Rate of sickle cell crises per 48 weeks: L-glutamine 2 vs. placebo 2.5; hazard ratio: 0.87 (95% CI: 0.63, 1.19)]. Comparatively, the relative risk of 0.56 [95% CI: 0.41, 0.77] was estimated for patients administered a total daily dose of 30 grams.
- A subgroup analysis in pediatrics similarly suggests that pediatrics patients may not receive similar benefit as compared to adult patients and most pediatric patients were administered 10 grams or 20 grams per day.
- No PK and PD data was collected during the phase III trial or the phase II trial to support the proposed dose.

Therefore, the Applicant should conduct an additional study to optimize the dose in adult and pediatric patients with body weight ≤ 65 kg as a PMC. The changes in the ratio of NADH to total NAD levels from the baseline should be measured in this study to support the dose optimization along with measures of efficacy and safety. The study population should reflect the typical population of patients with SCD in the United States, especially regarding renal and hepatic function.

2.4 Summary of Labeling Recommendations

In general, the Applicant has provided adequate clinical pharmacology information to support the product labeling. The following labeling concepts were recommended to be included in the final labeling.

- Section 2 should include instructions consistent with the conduct of the phase II and phase III trials regarding administration with food or beverage.
- (b) (4)
- Section 12.3 should include a description of pharmacokinetics of L-glutamine oral powder following a single oral or intravenous dose and a statement indicating that no studies have been conducted to assess the potential for drug interactions or the effect of various intrinsic factors on the PK or PD of L-glutamine powder as described in the Nutrestore labeling.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

L-glutamine oral powder was approved for the treatment of SBS in June 2004. The recommended dose is 30 grams per day mixed with water and taken with food.

FDA granted orphan-drug (08/01/2001) and fast-track (01/07/2005) designations for L-glutamine oral powder for the treatment of SCD. (b) (4)

The mechanism of action of L-glutamine in treating SCD is not fully understood. L-glutamine may improve the NAD redox potential in sickle RBC through increasing the availability of reduced glutathione. The effects of L-glutamine on redox potential in sickle cells may improve clinical response.

L-glutamine is a naturally occurring amino acid with a molecular weight of 146 g per mole. L-glutamine is available as 5 g of oral powder per paper-foil-plastic laminate packet. The to-be-marketed drug product was administered in the phase III trial (Study GLUSCC09-01) and the phase II trial (Study 10478).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action is not fully understood. The Applicant provided publically available literature to support the effect of L-glutamine on sickle RBC. The Applicant concluded that oral administration of L-glutamine results in normalization of the ratio of NADH to total NAD levels in sickle RBC (Niihara et al, 1998) and that the oral administration of L-glutamine significantly decreases endothelial cell adhesion of sickle RBC (Niihara et al, 2005). The Applicant hypothesizes that these effects will provide a clinically protective effect in patients with SCD.
Pharmacodynamics	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. L-glutamine powder was mixed with a glass of water, juice, or soft drink.
General Information	
Bioanalysis	Not applicable; no PK samples were collected in the trials submitted in support of the proposed indication.
PK Model	
Drug Exposure at Steady State	
Dose Linearity	Oral glutamine administration increased plasma glutamine levels in a dose-dependent manner.
Intrinsic & Extrinsic Factors	The effect of body weight, food or organ impairment on the PK or PD was not evaluated. Body weight does not appear to affect safety.
ADME	
Absorption	Following a single oral dose of 0.1 g/kg, the mean peak concentration was 1028 µM (or 150 µg/mL) which occurred 30 minutes after administration. An oral glutamine dose of 0.3 g/kg (the equivalent of 18 to 32 g) resulted in a mean peak plasma concentration of 1328 ± 99 µmol/L which occurred 45 minutes after administration. The PK following multiple oral doses has not been characterized. The effect of food or temperature has not been evaluated.
Distribution	After an intravenous bolus dose, the volume of distribution is 200 mL/kg.

Elimination	After an intravenous bolus dose, the terminal half-life is one hour. Exogenous L-glutamine is anticipated to undergo similar metabolism as endogenous L-glutamine. It participates in various metabolic activities, including the formation of glutamate, and synthesis of proteins, nucleotides, and amino sugars. L-glutamine is eliminated by glomerular filtration, but it is reabsorbed by the renal tubules.
DDI	No studies.
QT	
Impact of exposure on QT interval	Not evaluated.

3.3 Clinical Pharmacology Review Questions

3.3.1 How does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

No clinical pharmacology information is available from the pivotal phase III trial or the supportive phase II trial to support the safety and effectiveness of L-glutamine oral powder for the treatment of SCD. PK or PD samples were not collected in these clinical trials. The dosing regimen administered in these trials was based on a single dose finding trial (Study 8288).

Dose Selection

The Applicant conducted a single dose finding trial (Study 8288) in which the changes in the ratio of NADH levels to total NAD levels (redox potential) from the baseline were measured in 11 adults with SCD. The results of this trial demonstrated that a dose of 30 grams per day showed a consistent increase in mean redox potential. No significant changes were observed in the other dosing groups (10 grams per day or 20 grams per day). The Applicant stated that a dose of 30 grams per day provided consistent improvement in the redox potential to near normal and normal range (50% to 60%) or above (Niihara et al 1998).

In the pivotal phase III trial and supportive phase II trial, the Applicant administered a weight based dose of 0.3 g per kg, in which patients with body weight ≤ 65 kg were administered total daily doses of 10 grams or 20 grams. The Applicant did not provide a rationale for the administered dose in the application, including the protocols of the clinical trials; the Applicant simply stated that the widely used dose of 0.3 mg/kg was administered in the trials. A total daily dose of 10 grams or 20 grams did not affect NAD redox potential in adults with SCD. It is unknown if these doses can provide meaningful increases in NAD redox potential in pediatric or adult patients weighing less than the adults included in the dose finding trial (the median weight is unknown). The efficacy data (FDA analysis) from the phase III trial suggests that patients with body weight ≤ 65 kg or ≤ 18 years and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day may not benefit from L-glutamine compared to placebo as detailed below.

For comparison, the recommended dose for patients with SBS is 30 grams per day (0.3 g/kg) in divided doses mixed in water with food. The projected dietary intake from animal and plant protein is about 5 g to 10 g per day (Original NDA, clinical pharmacology review).

Pivotal phase III trial GLUSCC09-01

The results of the primary analysis demonstrated statistically significantly fewer (p = 0.0052) crises in favor of the L-glutamine (N= 151) relative to placebo (N=78). The median number of crises in the patients administered L-glutamine was 25% less or one less crises within the 48 week period compared to patients administered placebo. The sensitivity analyses intended to test the effect of imputation methods supported the primary analysis. The Applicant also concluded that patients administered L-glutamine had fewer hospitalizations and emergency room visits during the 48-week trial. A subgroup analysis suggests that L-glutamine does not reduce the frequency of crises relative to placebo in patients with body weight ≤ 65 kg and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day. The relative risk of a crisis, L-glutamine (N=100) vs placebo (N=52), was 0.87 [95% CI: 0.63, 1.19]. A PMC will be issued to recommend that the Applicant conduct a 24-week clinical trial in adult and pediatric patients to determine a dose that increases the ratio of NADH to total NAD levels from the baseline to a similar extend and provides similar efficacy and safety in patients ≤ 65 kg as compared to a patients > 65 kg administered a total daily dose of 30 grams.

Fewer adverse events, including sickle cell anemia with crises and acute chest syndrome, were observed for patients administered L-glutamine. Pediatrics had similar trend as adults in treatment emergent adverse events following administration of placebo and L-glutamine. A comparison of adverse reactions by weight buckets (10 kg for each bin) was conducted in patients treated with L-glutamine vs. placebo. The results suggest that similar safety profiles for patients in each weight bucket.

Please refer to the review of the safety and efficacy data by the clinical and statistical review teams for additional information regarding these analyses.

Supportive phase II trial 10478

The results of the primary analysis showed no differences between treatment groups; however, the sensitivity analyses intended to test the effect of imputation methods showed that the median number of crises for patients administered L-glutamine (N=37) was 33% to 50% lower relative to the placebo (N=33). No subgroup analyses based on age or weight were completed.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. Although the proposed total daily dose based on actual bodyweight: 10 grams for patients less than 30 kg, 20 grams for patients 30 kg to 65 kg, or 30 grams for patients greater than 65 kg) generally appears acceptable based on the efficacy and safety data from the pivotal phase III trial and the supportive phase II trial in the total population, the results of a subgroup analysis of the data from the phase III trial and the dose finding study suggest that a total daily dose of 10 grams or 20 grams may not effective. A PMC will be issued to recommend that the Applicant conduct a study to optimize the dose for patients with body weight ≤ 65 kg. See Dose Selection in section 3.3.1 above.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternative dosing regimen is not recommended based on intrinsic factors with the exception of weight. PK and PD samples were not collected in the pivotal phase III trial and the supportive phase II trial.

A clinical study to determine an appropriate dose in patients with hepatic impairment is not recommended. Glutamine is an amino acid that undergoes metabolism with most of its metabolism in intestine (Original NDA, clinical pharmacology review). Other organs including liver, kidney and immune system may contribute to its elimination. Additionally, the proposed dose is within the middle of the linear PK range studied in humans. Because hepatic metabolism or excretion does not account for a substantial portion of L-glutamine metabolism and L-glutamine is not a narrow therapeutic drug, a clinical study to evaluate the impact of hepatic impairment on the efficacy and safety of L-glutamine for the proposed indication will not be recommended.

A clinical study to determine an appropriate dose in patients with renal impairment is not recommended. Although L-glutamine is eliminated by glomerular filtration, it is reabsorbed by the renal tubules. Additionally, L-glutamine elimination is mostly through metabolism and the kidney is not a major organ that contributes to L-glutamine elimination. Lastly, substantial changes in L-glutamine exposure and the incidence of adverse reactions is not anticipated based on the recommended dose, observed tolerability and the known elimination pathways, although L-glutamine is for chronic administration in a patient population with the potential for renal insufficiency. Therefore, a clinical study to evaluate the impact of renal impairment on the safety of L-glutamine for the proposed indication will not be recommended.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The effect of food and the potential for drug interactions has not been evaluated.

The labeling will state that L-glutamine oral powder is to be mixed with cold or room temperature beverage or food as instructed in the phase III and phase II trials. The stability study results showed the recoveries for L-glutamine are greater than 90% for up to 4 hours after mixing with all of the beverages and foods recommended by the proposed labeling. The proposed administration of L-glutamine with beverage and food in the labeling was utilized in the pivotal trial and supportive trial. In addition, L-glutamine is administered with meal and snack in the labeling of NutreStore for SBS indication. The available data didn't suggest beverage or food could significantly decrease the bioavailability of L-glutamine. Therefore, it is not necessary to evaluate the impact of food on the efficacy and safety of L-glutamine for the proposed indication.

The potential for drug interactions is low, because the metabolism of glutamine is not mediated by common phase I or phase II metabolizing enzymes or transport proteins.

4. APPENDICES

None.

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/s/

YUHONG CHEN
05/31/2017

STACY S SHORD
05/31/2017

NAM ATIQUR RAHMAN
05/31/2017
I concur.