

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208587Orig1s000

OTHER REVIEW(S)

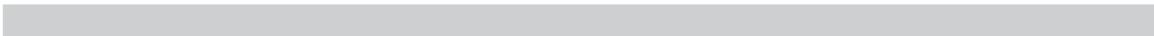
505(b)(2) ASSESSMENT

Application Information		
NDA # 208587	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Endari Established/Proper Name: L-glutamine Dosage Form: powder Strengths: 5 grams		
Applicant: Emmaus Medical		
Date of Receipt: September 7, 2016		
PDUFA Goal Date: July 7, 2017		Action Goal Date (if different):
RPM: Michael Gwathmey		
Proposed Indication(s): To reduce the acute complications of sickle cell disease in adult and pediatric patients five years of age and older.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
The application relies on the publicly available scientific literature.	

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The biopharmaceutics of L-glutamine has been described in 9 published studies, which include a study in very-low-birth-weight infants and intensive care unit (ICU) subjects on renal replacement therapy. The studies cover a range of L-glutamine doses that include the proposed oral L-glutamine dose of 30 g/d. These studies clearly establish the range of bioavailability of orally administered L-glutamine.

Collectively, the results of these 9 biopharmaceutic studies established the range of bioavailability of L-glutamine. Although the majority of orally administered L-glutamine is captured by the splanchnic circulation organs, there was no indication of any issue related to bioavailability that might affect efficacy and/or safety of the formulation of L-glutamine in the SCD product.

Because NutreStore and the proposed drug product are the same except for differences in labeling, the stability data for NutreStore was used to support the proposed drug product shelf life.

The applicant proposed to rely on available data from published literatures and NutreStore labeling to support the pharmacokinetics labeling of L-glutamine. The literature submitted by the applicant to support the pharmacokinetics labeling of L-glutamine is the same as the literature that supported the pharmacokinetics labeling of NutreStore. No

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

additional published literature is available that describes the pharmacokinetics characteristics of L-glutamine.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES," list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “NO” to (a) proceed to question #11.

If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

The PE is the applicant's own NDA

If this application relies only on non product-specific published literature, answer "N/A" If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A" If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): US 5693671 A

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

MICHAEL V GWATHMEY
07/07/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 3, 2017
Requesting Office or Division: Division of Hematology Products
Application Type and Number: NDA 208587
Product Name and Strength: L-glutamine 5 grams/packet
Applicant/Sponsor Name: Emmaus Medical, Inc.
Submission Date: June 29, 2017
OSE RCM #: 2016-2175-03
DMEPA Primary Reviewer: Idalia E. Rychlik, PharmD.
DMEPA Team Leader: Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Hematology Products requested that we review the revised Carton and Container Labeling for L-Glutamine oral powder (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^{a b c}

2 CONCLUSION

The revised carton and container labels are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Rychlik, I. Label and Labeling Review for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 23. RCM No.: 2017-2175.

^b Rychlik, I. Label and Labeling Review Memo for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 02. RCM No.: 2017-2175-01.

^c Rychlik, I. Label and Labeling Review Memo for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 30. RCM No.: 2017-2175-02.

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/s/

IDALIA E RYCHLIK
07/03/2017

HINA S MEHTA
07/05/2017

PMR/PMC Development Template

NDA # 208587
Product: Endari (L-glutamine)

PMC 3237-1
Description: Design and conduct a dose-finding trial in adult and pediatric patients with body weight less than or equal to 65 kg. The primary endpoint should be the increase in the ratio of NADH to total NAD levels from the baseline. The trial should have dose-finding and safety observation parts. The duration of evaluation for the dose-finding and safety observation should be justified in the protocol. After the optimal dose is identified, the selected dose should be administered to adult and pediatric patients with body weight less than or equal to 65 kg for at least 24 weeks to assess safety and activity of the selected dose. The study population should include patients with renal and hepatic impairment.

Schedule Milestones: Draft Protocol Submission: 1/2018
Final Protocol Submission: 4/2018
Study Completion: 7/2020
Final Report Submission: 12/2020

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study or clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Dose levels of 10 grams per day and 20 grams per day 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 with sickle cell disease (SCD) based on the results of the dose-finding study (Study 8288). The increase in the ratio of NADH to total NAD levels from the baseline is the foundation of Applicant’s hypothesis that L-glutamine may be a promising treatment for SCD.
- The Applicant did not provide adequate justification for weight-based dose as done for the flat dose 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% confidence interval: 0.63, 1.19)].
- The efficacy data from the phase III trials suggests that pediatric patients may not benefit from L-glutamine compared to placebo; most pediatric patients were administered doses of 10 grams per day or 20 grams per day based on their body weight.
- No PK and or PD data was collected during the phase III trial or the phase II trial to support the proposed dose.

3. If the study or clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to optimize the dose in patients with body weight ≤ 65 kg.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation):
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation):

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify):
- Other:

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study or clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized, controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

BARRY W MILLER
07/05/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 22, 2017
Requesting Office or Division: Division of Hematology Products
Application Type and Number: NDA 208587
Product Name and Strength: L-glutamine 5 grams/packet
Applicant/Sponsor Name: Emmaus Medical Inc
Submission Date: June 19, 2017
OSE RCM #: 2016-2175-02
DMEPA Primary Reviewer: Idalia E. Rychlik, PharmD.
DMEPA Team Leader: Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Hematology Products requested that we review the revised Carton and Container Labeling for L-Glutamine oral powder (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memo^{a b}

2 CONCLUSION

The revised carton and container labels are unacceptable from a medication error perspective. The prominence of the prescription only statement should be decreased and relocated for readability of other prominent information..

^a Rychlik, I. Label and Labeling Review for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 23. RCM No.: 2017-2175.

^b Rychlik, I. Label and Labeling Review Memo for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 02. RCM No.: 2017-2175-01.

3 RECOMMENDATIONS FOR EMMAUS MEDICAL INC

We recommend the following be implemented to both carton and container packaging prior to approval of this NDA 208587:

A. Carton Labeling and Container Label

- I. Significantly reduce the font size of the “Rx Only” statement and relocate it away from the establish name and product strength information to improve the prominence and readability of other important information.

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/s/

IDALIA E RYCHLIK
06/22/2017

HINA S MEHTA
06/23/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 6/20/17

To: Michael Gwathmey, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Katie Davis, Team Leader
OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for Endari™ (L-glutamine oral powder)
NDA 208587

In response to your labeling consult request dated October 27, 2016, we have reviewed the draft Package Insert and Carton/Container Labeling for Endari™ (L-glutamine oral powder) (Endari). This review is based upon the version of the draft PI and Carton/Container Labeling accessed from the share drive on June 19, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION	“Endari™ (L-glutamine oral powder)	Is this the correct format for the proprietary name and the established name and dosage form?
HIGHLIGHTS OF PRESCRIBING INFORMATION ADVERSE REACTIONS	“Most common adverse reactions (incidence (b) (4) 10%) are constipation, nausea, headache, abdominal pain, cough, pain in extremity, back	OPDP notes that Table 2 in the PI specifies that these are “Adverse Reactions Occurring at an Incidence (b) (4) 10%” (emphasis added). OPDP recommends deleting (b) (4) from the Highlights section in order to be consistent with Table 2.

	pain, and chest pain.” (emphasis added)	
6.1 Clinical Trials Experience	(b) (4)	OPDP recommends that the brand name “Endari” be used instead of “L-glutamine” in order to avoid distancing the serious AEs from the branded product. This is consistent with the recommendations made in the labeling review tool. As an editorial note, we note that the italicized “treatment” in the quote to the left has an extra ‘e’ in it.
6.1 Clinical Trials Experience	“Three deaths (3/187=1.6%) occurred during the study in the L-glutamine treatment group as compared to none in the placebo treatment group.”	Similar to our above comment, OPDP recommends that the brand name “Endari” be used instead of “L-glutamine.”
12. Mechanism of Action	(b) (4)	(b) (4)
14 Clinical Studies	(b) (4)	As this was an exploratory analysis, OPDP recommends revising this sentence to be less definitive, e.g., “. . . suggesting that over the entire 48-week period.” Additionally, OPDP recommends revising this presentation to include the absolute risk data in order to adequately qualify the presentation of the relative risk in the label. This is necessary in order to avoid promotional claims that may exaggerate the benefit of the drug by citing only the relative risk percentages without the accompanying absolute risk reduction (which is often much smaller). We also note that the specific data presented here does not directly correlate with the Clin/Stats review. We suggest ensuring that this data in the label is consistent with the FDA analysis.

Carton/Container Labeling

OPDP acknowledges and concurs with the January 23, 2017, and June 12, 2017, reviews of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RACHAEL E CONKLIN
06/20/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 12, 2017
Requesting Office or Division: Division of Hematology Products
Application Type and Number: NDA 208587
Product Name and Strength: L-glutamine 5 grams/packet
Applicant/Sponsor Name: Emmaus Medical Inc
Submission Date: March 2, 2017
OSE RCM #: 2016-2175-01
DMEPA Primary Reviewer: Idalia E. Rychlik, PharmD.
DMEPA Team Leader: Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Hematology Products requested that we review the revised Carton and Container Labeling for L-Glutamine oral powder (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton and container labels are unacceptable from a medication error perspective. The prominence of the prescription only statement should be decreased for readability of other prominent information, the conditionally acceptable name must be incorporated into the labels, and the product dosage form and mixing instructions must align with the prescribing information.

^a Rychlik, I. Label and Labeling Review for L-glutamine (NDA 208587). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 23. RCM No.: 2017-2175.

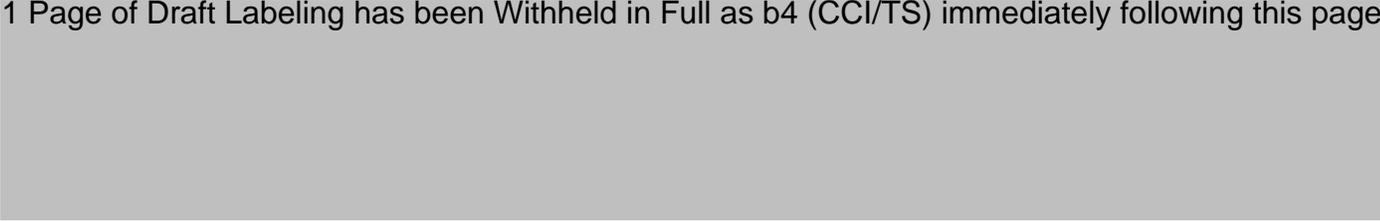
3 RECOMMENDATIONS FOR EMMAUS MEDICAL INC

We recommend the following be implemented to both carton and container packaging prior to approval of this NDA 208587:

A. Carton Labeling and Container Label

- I. Reduce the font size of the “Rx Only” statement and relocate it away from the product strength information to improve the prominence and readability of other important information.
- II. Replace the “Tradename” placeholder with the conditionally acceptability Proprietary Name.
- III. Align the product dosage form on the carton and container labels with the prescribing information. Replace (b) (4) with “L-glutamine oral powder”.
- IV. Revise the mixing directions to “Mix the contents with cold or room temperature beverage or food immediately before dosing.”

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/s/

IDALIA E RYCHLIK
06/12/2017

HINA S MEHTA
06/12/2017

CLINICAL INSPECTION SUMMARY

Date	April 6, 2017
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Rosanna Setse, M.D., Ph.D., Medical Officer Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader Michael Gwathmey, Regulatory Project Manager Division of Hematology Products (DHP)
NDA	NDA 208587
Applicant	Emmaus Medical Inc.
Drug	L-glutamine
NME	No
Therapeutic Classification	Amino acid
Proposed Indication	Treatment of sickle cell disease
Consultation Request Date	November 28, 2016
Summary Goal Date	May 26, 2017
Action Goal Date	July 7, 2017
PDUFA Date	July 7, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Sadanandan, Sieger/Lasky, and Oneal) were selected for inspections for a Phase 3 Study, GLUSCC09-01, and one clinical site (Dr. Niihara) was selected for inspection for a Phase 2 Study, 10478, in patients with sickle cell disease for this application.

The primary efficacy endpoint and adverse event reporting are verifiable at all three inspected Phase 3 study clinical sites (Drs. Sadanandan and Sieger/ Lasky/ Oneal) and in the one clinical site (Dr. Niihara) inspected for the Phase 2 study. The study data from these inspected clinical sites are considered acceptable in support of the requested indication.

The final classification for inspections for Study GLUSCC09-01 of two clinical sites (Drs. Sadanandan and Sieger/ Lasky) is No Action Indicated (NAI) and the third clinical site, (Dr. Oneal) is Voluntary Action Indicated (VAI). The final classification for inspection for Study 10478 of one clinical site (Dr. Niihara) is VAI. A Form FDA 483 was issued at the two VAI sites (Drs. Oneal and Niihara) for protocol violations/deviations. These protocol violations and deviations were reported in the clinical study reports in the NDA submission.

2. BACKGROUND

Sickle cell disease (SCD) is a hereditary disorder that is associated with significant morbidity and mortality including painful crises, acute chest syndrome, infection, stroke, bone deformity, and multiple organ damage due to an increase in destruction of red blood cells (RBCs) and occlusion of the microvascular system. The most common types of SCD are sickle cell anemia (HbSS), sickle hemoglobin C disease (HbSC) and sickle β^0 thalassemia. Sickle cell anemia and sickle β^0 thalassemia are the most severe forms of the disease. HbS is caused by a mutation in the β -globin gene in which the 17th nucleotide is changed from thymine to adenine and the sixth amino acid in the β -globin chain becomes valine instead of glutamic acid. Abnormal hemoglobin distorts red blood cells into a sickle shape, leading to erythrocyte rigidity and causing anemia and vaso-occlusion. Patients with SCD start to have signs of the disease during the first year of life, usually around 5 months of age. Sickle cell painful crisis is the most common and potentially life-threatening vaso-occlusive complication of SCD, and is the leading cause of emergency room visits and hospital stays for people who have sickle cell anemia.

The current treatment of SCD is mainly supportive. The goals of treating sickle cell disease are to relieve pain, prevent infections, organ damage, and stroke, and to control complications. Blood transfusions are commonly used to treat worsening anemia and sickle cell complications, such as stroke. Chronic blood transfusions can cause iron overload. Bone marrow or stem cell transplant is the only curative therapy for SCD. However, bone marrow or stem cell transplants are mostly confined to children with HLA compatible siblings and are used only in cases of severe SCD for children who have minimal organ damage from the disease. The procedure also has transplantation-related risk and side effects. Hydroxyurea (DROXIA) is the only drug that has been approved by FDA since 1998 to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months). Hydroxyurea increases fetal hemoglobin level which prevents red blood cells from sickling and improves anemia. Hydroxyurea is a myelosuppressive agent and can cause neutropenia and thrombocytopenia that require monitoring blood counts regularly and dose adjustment during the treatment.

Glutamine is an amino acid and also serves as a precursor for nicotinamide adenosine dinucleotide (NAD). L-glutamine increases the NAD redox potential and NADH level in sickle RBC, which may result in improvement of sickle RBC adhesion to endothelial cells. L-glutamine for treating sickle cell disease was granted orphan drug designation by the Agency in 2001 and the development program for L-glutamine for an indication to reduce painful crises in patients with sickle cell disease was granted fast track designation in 2004.

The sponsor submitted this NDA as a 505(b)(2) application for L-glutamine for the indication for the treatment of sickle cell disease (SCD) in both adult and pediatric populations. The application references NutreStore® (L-glutamine powder for oral solution, also owned by Emmaus) as a listed drug that was previously approved for a different indication for the treatment of short bowel syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone.

The sponsor submitted two clinical trials to support the proposed indication. The two clinical trials included a Phase 3, randomized, placebo-controlled trial (Study GLUSCC09-01) and a Phase 2, randomized, placebo-controlled trial (Study 10478) in adult and pediatric patients with SCD.

DHP requested three clinical sites for inspections for Study GLUSCC09-01 and one clinical site for inspection for Study 10478 based on relatively high enrollment and efficacy results at these sites.

Study GLUSCC09-01

Title of the study: A Phase III, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle β^0 -Thalassemia

Study GLUSCC09-01 was a multicenter, randomized (2:1), double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy of oral L-glutamine in patients with sickle cell anemia or sickle β^0 -thalassemia who were at least 5 years old.

The primary objective of the study was to evaluate the efficacy of oral L-glutamine as a therapy for sickle cell anemia and sickle β^0 -thalassemia as evaluated by the number of occurrences of sickle cell crises.

The primary efficacy endpoint was the number of sickle cell crises through Week 48 and prior to start of taper. A sickle cell crisis was defined as a visit to an emergency room/medical facility for sickle cell disease-related pain that was treated with a parenterally administered narcotic or parenterally administered toradol (ketorolac). Visits to facilities in which only non-narcotics or orally administered narcotics were used were counted as crises so long as non-narcotic pain relievers or oral narcotics were administered during the visit and the non-use of parenteral narcotic or parenteral toradol (ketorolac) was clearly documented in the source documents as a facility policy. In addition, the occurrence of chest syndrome (acute clinical pulmonary findings corroborated by findings of a new pulmonary infiltrate on chest X-ray films), priapism, and splenic sequestration were considered sickle cell crises even if the symptoms were not painful enough to require narcotics or toradol (ketorolac). Splenic sequestration was defined as an increase in spleen size associated with pain in the area of the organ along with a decrease in the hemoglobin concentration of at least 2 g/dL within a 24-hour period.

Eligible criteria included patients with sickle cell anemia or sickle β^0 -thalassemia, age of 5 years or older, history of at least 2 documented episodes of sickle painful crises within 12 months of the screening visit, without significant medical conditions (requiring prolonged treatment and/or hospitalization) within two months of the screening visit, no liver or renal insufficiency, no receipt of any blood products within three weeks of the screening visit, no treatment with other anti-sickling agents within 30 days of the screening visit or if they are on chronic therapy with an anti-sickling agent such as hydroxyurea at the time of screening, they have been on it for at least three months with intention of continuing it for the next fourteen months. Exclusion criteria also included international normalized ratio (INR) > 2.0 and serum albumin < 3.0 g/dL.

Study GLUSCC09-01 was conducted in 31 centers in United States. The date of the first enrollment was June 21, 2010, and the last subject completed in December 19, 2013.

Study 10478

A Phase II, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle β^0 -Thalassemia

Study 10478 was a Phase 2, multicenter randomized (1:1), double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of oral L-glutamine therapy for patients with sickle cell anemia or sickle β^0 -thalassemia who are at least 5 years old.

The primary objective of the study was to evaluate the efficacy of oral L-glutamine in therapy of sickle cell anemia and sickle β^0 -thalassemia as evaluated by number of occurrences of painful sickle cell crises.

The primary efficacy endpoint is the number of painful sickle cell crises through Week 48 and prior to start of taper.

Eligibility criteria included patients with sickle cell anemia or sickle β^0 -thalassemia, age of 5 years or older, history of at least 2 episodes of painful crises within 12 months of the screening visit, without significant medical conditions (requiring prolonged treatment and/or hospitalization) within two months of the screening visit, no liver or renal insufficiency, no receipt of any blood products within three weeks of the screening visit, no treatment with other anti-sickling agents within 30 days of the screening visit or if they are on chronic therapy with an anti-sickling agent such as hydroxyurea at the time of screening, they have been on it for at least three months with intention of continuing it for the next fourteen months. Exclusion criteria also included diabetes with untreated fasting blood glucose >115 mg/dL, international normalized ratio (INR) > 2.0, and serum albumin <3.0 g/dL.

Study 10478 was conducted in five centers in United States. The date of the first enrollment was April 23, 2004, and the last subject completed in May 29, 2008.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Swayam Sadanandan, MD* The Brooklyn Hospital Center 121 DeKalb Avenue Tenth Floor Main Hospital Building Brooklyn, NY 11201	Site #14 Protocol GLUSCC09-01 Subjects=15	January 17-20, 2017	NAI
Patricia Ann Oneal, MD** Howard University Hospital Center for Sickle Cell Disease 1840 7th Street, NW Room 203 Washington, DC 20001	Site #2 Protocol GLUSCC09-01 Subjects=23	January 5-18, 2017	VAI
Lance Sieger, MD - Co-PI Joseph L. Lasky, MD - Co-PI Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center 1124 W. Carson Street, Bldg. N-25 Box 468 Torrance, CA 90502	Site #21 Protocol GLUSCC09-01 Subjects=11	February 1-3, 2017	NAI
Yutaka Niihara, MD, MPH Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center 1124 W. Carson Street Building E4, Room 30 Torrance, CA 90502	Site #101 Protocol 10478 Subjects=25	February 6-9, 13, 2016	VAI

* Dr. Swayam Sadanandan has retired. ** Dr. Patricia Ann Oneal is no longer with Howard University.

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators**1. Swayam Sadanandan, MD (Site #14, Protocol GLUSCC09-01, Brooklyn, NY)**

The site screened and enrolled 15 subjects for Study Protocol GLUSCC09-01. An audit of 15 enrolled subjects' records was conducted. Among the 15 subjects, 10 subjects completed the study and 5 subjects discontinued from the study (four subjects withdrew consent [2 each in L-glutamine and placebo group] and one subject in the placebo group was discontinued at

discretion of the clinical investigator due to noncompliance). The discontinuation data listing provided in the NDA was verified by review of source documents.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, electronic files, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted. All source data were generally verifiable at the site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Patricia Ann Oneal, M.D. (Site #2, Protocol GLUSCC09-01, Washington, DC)

The site screened 32 subjects and enrolled 23 subjects for Study Protocol GLUSCC09-01. An audit of 23 enrolled subjects' records was conducted. Among the 23 subjects, 12 subjects completed the study and 11 subjects discontinued from the study. Two of the eleven discontinued subjects (#504 and #516 in the L-glutamine group) had cardiac arrest and died from causes considered to be unrelated to study medication by the clinical investigator. The discontinuations and reasons for discontinuations reported in the NDA data listing were source verified.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted.

However, the following protocol violations/deviations were noted and a Form FDA 483 (Inspectional Observations) was issued at the site for failure to conduct an investigation in accordance with investigational plan and failure to prepare accurate case histories with respect to observations and data pertinent to the investigation:

- **Violations of inclusion criteria:** Two subjects were initially checked as eligible subjects but late corrected as not eligible subjects.

- One subject (#101, placebo group) was enrolled in the study later without further verification for requirement of 2 painful crises within 12 months. The subject discontinued from the study subsequently after identification. The enrollment log indicates that the subject moved out of state.
- One subject (#102, L-glutamine group) had sickle β^+ -Thalassemia as per the hemoglobin electrophoresis results, not sickle β^0 -Thalassemia as specified in eligibility criteria. The patient enrolled on 3/2/11 and received study treatment from 3/2/11 to 3/28/11. The investigator documented the hemoglobin electrophoresis result on 3/9/11 and reported to the study sponsor and IRB. The subject discontinued from the study thereafter.
- **Incorrect stratification for randomization:** One subject (#503, L-glutamine group) not currently using hydroxyurea (HU) treatment was incorrectly stratified for randomization with the hydroxyurea user group.
- **Incorrect dosing:** One subject (#104, L-glutamine group) was dispensed the incorrect amount of study medication based on body weight, 20 gram instead of 30 gram per day at visit 2. The dosage was corrected on visit 3/Week 4.
- **Incomplete or inaccurate recording:** Several incomplete or inaccurate recording of concomitant medications and action taken for adverse events were noted.
 - Two subjects (#505 and #513) had incomplete concomitant medications listing
 - Five subjects (#510, #513, # 514, #515, and #516) had inaccurate or incomplete records of action taking for experienced adverse events.

The above observations were shared with DHP. These protocol violations/deviations were reported in the clinical study report and submitted in the NDA submission. These protocol violations were observed in the initial enrollment period. The first two subjects (#101 and #102) were discontinued from the study shortly due to not meeting the inclusion criteria. These observations appear unlikely to have significant impact on overall efficacy and safety results.

In general, the efficacy and safety data at the site are verifiable and this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Lance Sieger, MD and Joseph Lasky, MD (Site #21, Protocol GLUSCC09-01, Torrance, CA)

The site screened 17 subjects and enrolled 11 subjects for Study Protocol GLUSCC09-01. An audit of 11 enrolled subjects' records was conducted. Among the 11 subjects, 8 subjects completed the study and 3 subjects (all in the L-glutamine group) discontinued from the study (due to reported adverse events). The three subject discontinuations were source verified during the inspection.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Yutaka Niihara, MD (Site #101, Protocol 10478, Torrance, CA)

The site screened 42 subjects and enrolled 25 subjects for Study Protocol 10478. An audit of 25 enrolled subjects' records was conducted. Among the 25 subjects, one subject withdrew consent and received no treatment. Of 24 subjects who received study treatment, 12 subjects completed the study and 12 subjects discontinued the study treatment. Of the twelve subjects who discontinued from study treatment, there was one death; subject (#015) in the L-glutamine group died of hypoglycaemia/altered level of consciousness. The discontinuation data listing submitted in the NDA was compared to source documents and verified.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted.

However, the following protocol violations/deviations were noted and a Form FDA 483 (Inspectional Observations) was issued at the site for failure to conduct an investigation in accordance with the investigational plan, specifically:

- Violations of inclusion criteria: Seven subjects who had <2 painful crises in the previous 12 months were enrolled in the study. The PI (previous sponsor for this investigator-initiated study) granted waiver for the enrollment.
- Deviations of exclusion criteria: Nineteen of 25 enrolled subjects had no INR tests to assess exclusion criterion of INR >2.0 (10 subjects in L-glutamine group and 9 subjects in placebo group). One subject had serum albumin <3.0 g/dL (Subject 014 in L-glutamine group) and one subject received blood product within 3 months were enrolled in the study (Subject 011 in placebo group).

The above observations were shared with DHP. These protocol violations/deviations were reported in the clinical study report and submitted in the NDA submission. Enrollment of subjects with <2 painful crises in the previous 12 months were observed in both the L-glutamine and the placebo groups. Seven subjects include three subjects in the L-glutamine group (Subjects 003, 017, and 027) and four subjects in the placebo group (Subjects 004, 010, 015 and 019). Four of seven subjects were pediatric patients [Subjects 003 (11 years), 017 (16 years), 004 (16 years) and 019 (15 years)]. The investigator/sponsor of the study granted waiver for these subjects to be enrolled in the trial, including the 4 pediatric subjects with known enrollment challenge. Since the primary efficacy endpoint was the number of sickle cell crises through Week 48 (not the change of painful crisis from baseline) and similar number of subjects with <2 painful crises in the previous 12 months were enrolled in both groups this observation appears unlikely to have significant impact on overall efficacy and safety results of the study. The protocol deviations for exclusion criteria appear to be minor and unlikely to be significant for the overall study results.

In general, the primary efficacy and safety data at the site are verifiable and this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of this specific indication.

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OSI/DCCE/GCP Reviewer/Min Lu

OSI/ GCP Program Analyst/Yolanda Patague

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/s/

MIN LU
05/02/2017

JANICE K POHLMAN
05/02/2017

KASSA AYALEW
05/02/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: January 23, 2017
Requesting Office or Division: Division of Hematology Products
Application Type and Number: NDA 208587
Product Name and Strength: L-glutamine 5 grams/packet
Product Type: Single Ingredient
Rx or OTC: RX
Applicant/Sponsor Name: Emmaus Medical Inc
Submission Date: September 7, 2016 and December 9, 2016
OSE RCM #: 2016-2175
DMEPA Primary Reviewer: Idalia E. Rychlik, PharmD.
DMEPA Team Leader: Hina Mehta, PharmD.

1 REASON FOR REVIEW

The Division of Hematology Products has requested DMEPA to review the label and labeling for NDA 208587 L-glutamine submitted by Emmaus Medical Inc. The application was submitted as a 505(b)(2) that makes reference to listed drug NutreStore (L-glutamine), NDA 021667. We have reviewed the proposed carton and container labeling and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed prescribing information (PI), container label and carton labeling for areas of vulnerability in regards to medication error. We identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the container label and carton labeling to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. PRESCRIBING INFORMATION (PI)

I. HIGHLIGHTS: DOSAGE AND ADMINISTRATION

1. Clarify administration statement to include volume of water or food recommended for reconstitution prior to consumption. For example, “Each dose should be reconstituted in 8 oz (250 mL) of cold or room temperature water or food”.

II. HIGHLIGHTS: DOSAGE FORMS AND STRENGTHS

1. Remove the type of administration statement as only the dosage form and strength should be included in this section, i.e remove “L-glutamine powder

(b) (4)

III. SECTION 2: DOSAGE AND ADMINISTRATION

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear in Section 11 and 12.3 of the PI. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, replace the symbols “<” and “>” with their intended meanings to prevent misinterpretation and confusion throughout the prescribing information.
2. Revise the statement (b) (4) to use positive language. E.g. “mix with cold or room temperature food or beverage”.
3. Remove, place statement in another section or bullet point the (b) (4) (b) (4) statement. As currently presented it may lead to confusion.
4. Clarify administration statement to include volume of water or food recommended for reconstitution prior to consumption. For example, “Each dose should be reconstituted in 8 oz. (250 mL) of cold or room temperature water or food”

IV. SECTION 11 and 12.3: DESCRIPTION, PHARMACOKINETICS

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear in Section 11 and 12.3 of the PI. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows: Replace all “µg” symbols appearing in the PI with “mcg”.

4.2 RECOMMENDATIONS FOR EMMAUS MEDICAL INC

We recommend the following be implemented prior to approval of this NDA 208587:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine powder (b) (4).
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement (b) (4) to use positive language. E.g. “mix with cold or room temperature food or beverage”.
5. Remove bold font on manufacturer information as it takes reader’s attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.7.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for TRADENAME (L-glutamine) that Emmaus Medical Inc submitted on September 7, 2016 and the listed drug (LD).

Table 2. Relevant Product Information for TRADENAME (L-glutamine) and the Listed Drug		
Product Name	L-glutamine	NutraStore (L-glutamine)
Initial Approval Date	N/A	2004
Active Ingredient	L-glutamine	
Indication	Sickle Cell Disease	Treatment of Short Bowel Syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone.
Route of Administration	oral	
Dosage Form	Powder (b) (4)	
Strength	5 grams	
Dose and Frequency	0.3 g/kg twice daily	30 g daily in divided doses (5 g taken 6 times each day orally) for up to 16 weeks
How Supplied	(b) (4) paper-foil-plastic laminate packets	
Storage	25°C (77°F)	15°-30°C (59°-86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 15, 2016, we searched the L:drive and AIMS using the terms, L-glutamine and NutraStore to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 0 previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 15, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: NutraStore (L-glutamine) Match Any of the Words: NutraStore (L-glutamine)

D.2 Results

Our search resulted in 0 relevant safety articles.

APPENDIX G. LABELS AND LABELING

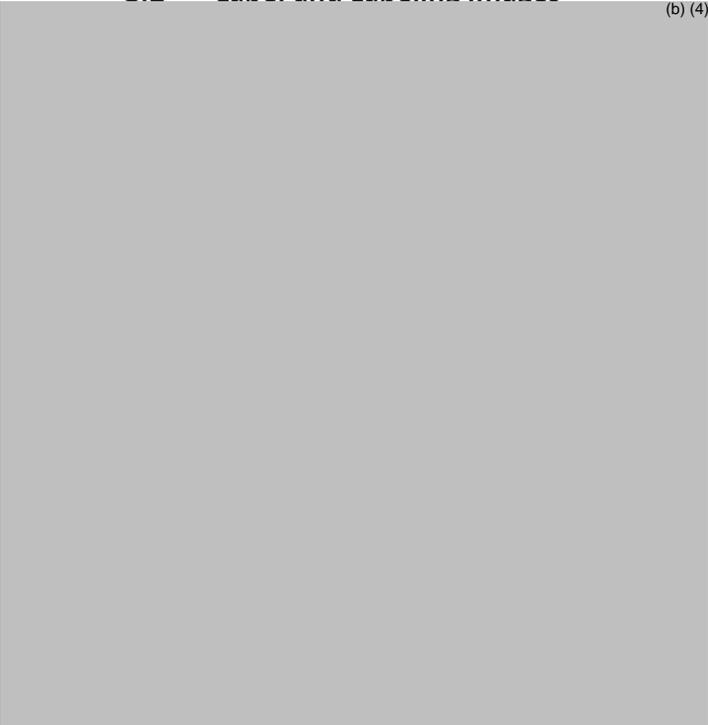
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following TRADENAME (L-glutamine) labels and labeling submitted by Emmaus Medical Inc on September 7, 2016.

- Container label
- Carton labeling
- Prescribing Information (PI)

G.2 Label and Labeling Images

(b) (4)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IDALIA E RYCHLIK
01/23/2017

HINA S MEHTA
01/24/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208587

Application Type: New NDA

Drug Name(s)/Dosage Form(s): L-glutamine, 5 grams powder

Applicant: Emmaus Medical, Incorporated

Receipt Date: September 7, 2016

Goal Date: July 7, 2017

1. Regulatory History and Applicant's Main Proposals

Emmaus Medical Inc. has submitted a new NDA for oral powder L-glutamine as a 505(b)(2). The application makes reference to listed drug NutreStore (glutamine), NDA 021667, which is also owned by Emmaus. The proposed indication is for treatment of sickle cell disease in both adults and children, and Emmaus has Orphan Designation for this indication.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 9, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: Not in two-column format
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: Not contained in one-half page
- NO** 3. A horizontal line must separate:
 - HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).*Comment: horizontal line not present*
- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.
Comment:
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.
Comment:
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment:
- NO** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *Contraindication section not present (n/a to Box Warning and Recent Major Changes)*

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment: *No BW*

Selected Requirements of Prescribing Information

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment: *No BW*

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment: *No BW*

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment: *No BW*

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *No RMC*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment: *No RMC*

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *Only one dosage form*

Contraindications in Highlights

- NO** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment: *No Contraindication Section*

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- NO** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment: *Not right justified*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- NO** 24. The TOC should be in a two-column format.
Comment: Not in two-column format
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: No BW
- NO** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment: Not all section heading are bolded
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment: Section 15 not included

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Section 8 is not in PLLR.

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment: No cross-referecning noted

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment: No RMC's noted

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment: No BW

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment: No BW

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment: Contraindications are listed.

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“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.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: No Post Marketing adverse reactions information listed

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *There is not patient information provided in the application although they reference it. This section will need other revisions.*

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

MICHAEL V GWATHMEY
11/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208587	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: L-glutamine Established/Proper Name: to be determined Dosage Form: powder Strengths: 5 grams		
Applicant: Emmaus Medical Inc. Agent for Applicant (if applicable): n/a		
Date of Application: September 7, 2016 Date of Receipt: September 7, 2016 Date clock started after Unacceptable for Filing (UN): n/a		
PDUFA/BsUFA Goal Date: July 7, 2017		Action Goal Date (if different):
Filing Date: November 6, 2016		Date of Filing Meeting: October 21, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment for sickle cell disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<i>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i>	
<i>• The product is a Qualified Infectious Disease Product (QIDP)</i>	
<i>• A Tropical Disease Priority Review Voucher was submitted</i>	
<i>• A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 053841

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Product/Indication has Orphan Designation and therefore iPSP does not apply.
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input type="checkbox"/>	<input checked="" type="checkbox"/>		PLR format requires that the Highlights section be in a two-column format and be contained within ½ page.
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input type="checkbox"/> <input type="checkbox"/>	<input checked="" type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?				
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 11/19/2001, 4/20/2009	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6/11/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 21, 2016

BACKGROUND: Emmaus Medical Inc. submitted a new NDA for oral powder L-glutamine. The application has been submitted as a 505(b)(2) that makes reference to listed drug NutreStore (glutamine), NDA 021667, which is also owned by Emmaus. The proposed indication is for treatment of sickle cell disease in both adults and children. Emmaus has Orphan Designation for this indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Gwathmey	Y
	CPMS/TL:	Amy Baird, Mara Miller	Y
Cross-Discipline Team Leader (CDTL)	Kathy Robie Suh		Y
Division Director/Deputy	Ann Farrell/Ed Kaminskas		Y
Office Director/Deputy			
Clinical	Reviewer:	Rosanna Setse	Y
	TL:	Kathy Robie Suh	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Yuhong Chen	Y
	TL:	Stacy Shord	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		

Biostatistics	Reviewer:	Che Smith	Y
	TL:	Yuan-Li Shen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luan Lee	Y
	TL:	Christopher Sheth	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Rajan Pragani	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Rajan Pragani	
• Drug Product	Reviewer:	Rajan Pragani	
• Process	Reviewer:	Zhaoyang Meng	
• Microbiology	Reviewer:		
• Facility	Reviewer:	Ephrem Hunde	
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Rachael (Ray) Conklin	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Hina Mehta	N
	TL:	Idalia Rychlik	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			
*For additional lines, right click here and select "insert rows below"			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Relies on the publicly available scientific literature to describe the biopharmaceutics of L-glutamine. The composition and the manufacturing process for the L-glutamine drug product for the treatment of SCD are the same as those used in approved product NutreStore® in NDA 21,667.</p>
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

If no, explain:	
<ul style="list-style-type: none"> Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined An AC meeting will probably be needed, but will discuss more as the review continues
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ann Farrell, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Mid-Cycle: 2/6/17; Wrap-Up: 6/1/17; Primary Reviews: 6/2/17; Secondary Reviews: 6/9/17; CDTL Review: 6/17/17; PDUFA: 7/7/17	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

MICHAEL V GWATHMEY
11/04/2016

MARA B MILLER
11/04/2016