

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208587Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 208587

Review #1

Drug Name/Dosage Form	L-glutamine Oral Powder
Strength	5 grams
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Emmaus Medical, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Original</i>	<i>9/7/16</i>	<i>All</i>
<i>Amendment 2</i>	<i>10/18/16</i>	<i>DP/EA</i>
<i>Amendment 23</i>	<i>5/5/17</i>	<i>DS/DP</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rajan Pragani	ONDP/DNDAPI/Branch 1
Drug Product	Rajan Pragani	ONDP/DNDAPI/Branch 1
Process	Zhaoyang Meng	OPF/DPAI/PABII
Microbiology	Rajan Pragani	ONDP/DNDAPI/Branch 1
Facility	Ephrem Hunde	OPF/DIA/IABI
Biopharmaceutics	n/a	
Regulatory Business Process Manager	Rabiya Laiq	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Rajan Pragani	ONDP/DNDAPI/Branch 1
Laboratory (OTR)	n/a	
ORA Lead	Katherine Jacobitz	OPQO/DPQOIV/PQIB
Environmental	Rajan Pragani	ONDP/DNDAPI/Branch 1

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	01/26/2017	
	Type II		Adequate	1/27/2017		
	Type III		n/a	No review	Adequate information in NDA	
	Type III		n/a	No review	Adequate information in NDA	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	053841	Initial IND
NDA	021667	Stability data is relied upon for this 505(b)(2) application. Drug product in this NDA is exactly same except for labeling.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 208587 for Endari (L-glutamine oral powder), 5 grams per paper-foil-plastic laminate packet.

As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance for storage at (b) (4). OPQ grants a 48 month drug product expiration period for storage at 25°C ± 2°C/60% RH (b) (4) RH in the commercial packaging.

II. Summary of Quality Assessments

A. Product Overview

The drug product Endari is L-glutamine crystalline powder packaged in a foil packet for the treatment of sickle cell disease (SCD). SCD is a debilitating chronic disease that currently has only one FDA-approved treatment - hydroxyurea. FDA has acknowledged that this 505(b)(2) submission is for a rare disease and was given orphan designation.

OPQ considers all review issues adequately addressed. The potential risks to patient safety, product efficacy, and product quality appropriately mitigated. The manufacturing and control strategy are adequate for the production of quality drug product on a commercial scale.

Therefore, OPQ recommends APPROVAL of NDA 208587 and grants a (b) (4) month re-test period for the drug substance for storage at (b) (4) and a 48 month drug product expiration period for storage at 25°C ± 2°C/60% RH (b) (4) in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	<i>Sickle Cell Disease</i>
Duration of Treatment	<i>chronic</i>
Maximum Daily Dose	<i>30 grams per day (based on body weight)</i>
Alternative Methods of Administration	<i>n/a</i>

B. Quality Assessment Overview

Drug Substance

(b) (4)

With regard to the (b) (4) HPLC stress test that was a concern of the (b) (4) it should be noted that the applicant would improve the specificity of this experiment post-approval. This was stated in an amendment in response to an information request.

The applicant's proposed (b) (4)-month retest date can be granted to the drug substance when stored at (b) (4) in the proposed container closure (b) (4)

Drug Product

The drug product is 5 grams of L-glutamine drug substance packaged in a foil packet. There are no additional excipients. The drug product is to be administered orally in increments of 5 grams with an upper limit of 30 g/day, administered twice daily. The L-glutamine powder should be mixed immediately before ingestion with water or any (b) (4) beverage other than alcohol or with any (b) (4) food such as yogurt, applesauce, (b) (4). Complete dissolution is not required prior to administration.

The primary container closure system is (b) (4) packet with (b) (4) paper-foil-plastic laminate. The filled, sealed packets are packaged in pharmacy dispensing packs, which are cardboard containers.

The applicant's proposed 48-month expiry date can be granted to the drug product when stored at $25 \pm 5^{\circ}\text{C}/60\%$ RH in the proposed container closure (i.e., (b) (4))

Process

(b) (4)

Quality Microbiology

The drug product is a non-sterile, dry powder that is controlled by release testing for bioburden in the drug substance and drug product. The drug product on storage is protected from moisture by a foil packet and monitored for moisture and bioburden.

Biopharmaceutics

Because the drug product is just the amino acid L-glutamine powder for oral administration, a biopharmaceutics review was deemed unnecessary.

Facilities

(b) (4)

The non-concur memo is attached to the appendix of this IQA.

Nothing unusual was noted for the other facilities. Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing and testing facilities for NDA 208587 are found to be acceptable.

Environmental Assessment

The applicant includes language complying with 21 CFR 25.31 (b), stating that no extraordinary circumstances “exist that would warrant preparation of an environmental assessment.” This NDA also qualifies for 21 CFR 25.31 (c) as an amino acid.

C. Special Product Quality Labeling Recommendations (NDA only)

[Redacted content]

D. Final Risk Assessment (see Attachment)

[Redacted content]



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LABELING

R Regional Information

1.14 Labeling

Immediate Container Label



DMEPA has communicated with the applicant (06/12/2017) to do the following for the Container Label and Carton Labeling (waiting for a response):

1. 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.
2. Replace the “Tradename” placeholder with the conditionally acceptability Proprietary Name.
3. Align the product dosage form on the carton and container labels with the prescribing information. Replace “(b) (4)” with “L-glutamine oral powder”.
4. Revise the mixing directions to “Mix the contents with cold or room temperature beverage or food immediately before dosing.”

Reviewer’s Assessment: Adequate.

DMEPA has addressed deficiencies with the container label. The proposed container that would include DMEPA’s suggested revisions meets the regulatory requirement from a CMC perspective. The storage conditions should be updated to comply with USP controlled room temperature, “Store at 20°C to 25°C (68°F to 77°F)”.

Carton Labeling

(b) (4)

Reviewer's Assessment: Adequate.

DMEPA has addressed deficiencies with the carton labeling. The proposed carton that includes DMEPA's suggested revisions meets the regulatory requirement from a CMC perspective. The storage conditions should be updated to comply with USP controlled room temperature, "Store at 20°C to 25°C (68°F to 77°F)".

Package Insert

The CMC sections of the package insert (PI) are very similar to the drug product NutreStore (NDA 021667), which is L-glutamine oral powder in a foil packet from the same company that is used for another indication. Minor adjustments that differ from the NutreStore PI are listed below, and these recommendations are currently under review by the applicant.

HIGHLIGHTS

It was decided that this product would not be called [REDACTED] (b) (4) [REDACTED]. Instead, it will be referred to as “L-glutamine oral powder” for closest alignment to USP guidance. The dosage form is an “Oral Powder.”

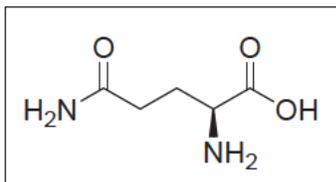
3 DOSAGE FORMS AND STRENGTHS

The dosage form was changed to “Oral Powder.” In addition, this section was modified by including white and crystalline in the description of the powder.

The strength (5 g) was accidentally deleted during edits and needs to be reintroduced.

11 DESCRIPTION

Minor adjustments to this section include subscripting numbers in the molecular formula, adding the units “g/mol,” and including stereochemistry in the structural formula as shown below (the previous picture of L-glutamine did not show stereochemistry).



16 HOW SUPPLIED/STORAGE AND HANDLING

This section was modified by including white and crystalline in the description of the L-glutamine powder. The storage conditions should be updated to comply with USP controlled room temperature, “Store at 20°C to 25°C (68°F to 77°F)”.

Reviewer’s Assessment: *Adequate.*

FDA recommendations for the proposed package insert are currently under review by the applicant. If the applicant accepts the CMC recommendations, the PI would meet the regulatory requirement from a CMC perspective. The storage conditions should be updated to comply with USP controlled room temperature, “Store at 20°C to 25°C (68°F to 77°F)”.

List of Deficiencies (after the applicant submits revised labeling, IR will be sent and memorandum will be added to cover changes):

1. Revise the storage conditions on the container labeling, carton labeling, and in the PI to read “Store at 20°C to 25°C (68°F to 77°F)” to be consistent with USP controlled room temperature.
2. In “3 Dosage Forms and Strengths” of the PI, include the strength (5 g).

Primary Labeling Reviewer Name and Date:

Rajan Pragani (see below for date)

Secondary Reviewer Name and Date:

Benjamin Stevens (see below for date)



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Memorandum

Date May 30, 2017

From Ephrem Hunde, PhD
Chemical Engineer, OPF Division of Inspectional Assessment, Branch 1

Subject Non Concurrence with withhold Recommendation for NDA 208587, L-glutamine powder

Thru Zhihao "Peter" Qiu, Branch Chief, OPF Division of Inspectional Assessment, Branch 1

To CMS WA # 162907

Applicant: Emmaus Medical, Inc.
21250 Hawthorne Blvd.
Torrance, USA 90503

Establishment: [REDACTED] (b) (4)

The Office of Process and Facility (OPF) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) conducted by [REDACTED] (b) (4) investigators from [REDACTED] (b) (4) facility. OPF has also reviewed the firm's [REDACTED] (b) (4) written response to the FDA Form-483 observations. This inspection was initiated by [REDACTED] (b) (4) to provide pre-approval coverage of NDA 208587 [REDACTED] (b) (4). [REDACTED] (b) (4) is named in NDA 208587 as the site for drug product testing.

OPF does not concur with the withhold recommendation for NDA 208587. [REDACTED] (b) (4) recommended withholding approval of this application due to product specific deficiencies. The following deficiencies specific to NDA 208587 were observed.

1. Observation 1: [REDACTED] (b) (4)

Firm's Response to Observation 1: [REDACTED] (b) (4)

(b) (4)

Drug Product Reviewer's comment: OPF/DIA obtained input from the Drug Product's reviewer that stated, although the USP methods were not demonstrated to be (b) (4) that were referenced in support of NDA 208587.

Conclusion: The firm's response is deemed acceptable.

2. Observation 2: (b) (4)

(b) (4)

Drug Product Reviewer's comment: OPF/DIA obtained input from the Drug Product's reviewer that stated (b) (4)

The applicant has committed to further method improvement, which is acceptable.

Conclusion: The firm's response and commitment to perform further method development studies are deemed acceptable.

OPQ/OPF Recommendation:

The product-specific observations are directly related to adequacy of methods validation. OPF consulted with the Drug Product Reviewer responsible for assessment of analytical methods filed in support of the application. Based on the above assessment of the inspection findings and the firm's response to Form 483 observations, OPF does not concur with the recommendation by the (b) (4) to withhold approval of NDA 208587, L-glutamine powder.

If you have any questions, please contact me at (240) 402-2321 or by email at ephrem.hunde@fda.hhs.gov.

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Ephrem Hunde, PhD
Chemical Engineer

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(b) (4)
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Rajan Pragani, PhD, ATL/ DP reviewer



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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product: NDA 208587 L-glutamine Oral Powder, 5g per packet (Non-high Risk Drug: solid, oral powder)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale and equipment • Site 	Low	End product testing	Acceptable	
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale and equipment • Site 	Low	No instability demonstrated for drug product through testing	Acceptable	
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale and equipment • Site 	Low	No excipients; crystalline powder in packet should be uniform	Acceptable	
Microbial limits	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale and 	Low	End product release testing of drug substance; water content is monitored in drug	Acceptable	

	<p>equipment</p> <ul style="list-style-type: none"> • Site 		<p>product; foil packet</p>		
Palatability	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale and equipment • Site 	Medium	<p>Bad taste was not mentioned in clinical trial; patients have the option to take L-glutamine with flavored food or drink</p>	Acceptable	



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