

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-667

CHEMISTRY REVIEW(S)

NDA 21-667

Nutrestore™(Glutamine Powder for Oral Solution)

Nutritional Restart Pharmaceutical, L.P.

Maria Ysern, MSc.

Division of Gastrointestinal and Coagulation Drug Products

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Chemistry Review Data Sheet

1. **NDA 21-667**
2. **REVIEW # 2**
3. **REVIEW DATE:** 27 April 2004
4. **REVIEWER:** Maria Ysern, MSc.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11 AUG 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	11 AUG 2004
Amendment BC	29 JAN 2004
Amendment BZ	13 MAY 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Nutritional Restart Pharmaceutical, L.P
220 Westpark Corporate Center
Address: South Alston Avenue
Durham, NC 27713
Representative: Cato Research
Telephone: (919) 361-2286

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nutrestore TM
- b) Non-Proprietary Name (USAN): L-Glutamine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard review

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Cotherapy with human growth hormone

11. DOSAGE FORM: Powder for oral solution

12. STRENGTH/POTENCY: 5 gram packet

13. ROUTE OF ADMINISTRATION: Oral

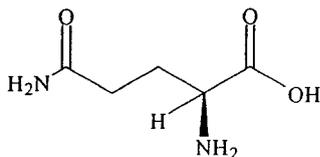
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	Cato Holding Co.	Oral Glutamine packets	1	Adequate		
—	II	Cato Holding Co.	Oral Glutamine Packets	1	Adequate		
—	II	—	L-Glutamine	1	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54,284	Somatropin for injection/glutamine
IND	48,750	Serostim[somatropin (rDNA origin)for injection

18. STATUS:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable from compliance		Office of Compliance
Pharm/Tox	Acceptable	May, 2004	Dr. Ke Zhang
Biopharm	Acceptable	June, 2004	Dr. Sue Lee
LNC	N/A		
Methods Validation ^a	N/A		
DMETS	No objections for Nutrestore™ from safety perspective	Feb 20, 2004	Kimberly Culley
EA ^b	N/A		
Microbiology	N/A		

^a Methods are USP

^b See page 13 of review notes

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review for NDA 21-667

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has adequately responded to the information request letter.

A copy of the specifications for the Drug Product and the Drug Substance was sent to the NDA, since they were only included in the corresponding DMFs. See pages 9 and 10 of this second review.

The labeling recommendations have been corrected as required. See page 11-13. of this review.

The cartons will be reviewed during the labeling discussion by the team.

The company has informed the agency that it is applying for an NDC number.

This NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

The information regarding the drug substance and the drug product are present in the following DMFs:

a. _____

b.

c. _____

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Is a white crystalline powder. The aminoacid glutamine is also known as (S)-2-aminoglutaramic acid, L-glutamic acid 5-amide, (S)-2,5, -diamino-5-oxopentanoic acid

Executive Summary Section

or L-Glutamine. The Molecular formula is $C_5H_{10}N_2O_3$ and the molecular weight is 146.15 d.

Drug Product:

Glutamine for Oral administration is formulated as a white crystalline powder in a paper-foil plastic laminate packet. There is no further processing or addition of excipients to the drug substance before it is packaged into the individual packets. Each packet contains 5 g of L-glutamine.

B. Description of How the Drug Product is Intended to be Used

Oral Glutamine should be administered in a divided daily dose of 30 g (5g taken 6 times each day orally).

It will be used as a co-therapy with subcutaneous [Somatropin (rDNA origin) for injection],-(recombinant human growth hormone) to reduce or eliminate the requirement for parenteral nutrition and to increase gut absorption of nutrients in patients with short bowel syndrome (SBS).

It will be used 6 times a day for four weeks. The treatment with Oral Glutamine should be continued to sustain the achieved increase in gut absorption and reduction of parenteral nutrition requirements.

C. Basis for Approvability or Not-Approval Recommendation

The information provided is sufficient to support the approval of this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Maria Ysern, MSc., HFD-180
 ChemistryTeamLeaderName/Liang Zhou, PhD, HFD-180
 ProjectManagerName/Tania Clayton

C. CC Block in DFS

7 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

A-1

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

/s/

Maria Ysern
6/4/04 03:19:40 PM
CHEMIST

Liang Zhou
6/4/04 03:47:59 PM
CHEMIST

NDA 21-667

Nutrestore™(Glutamine Powder for Oral Solution)

Nutritional Restart Pharmaceutical, L.P.

Maria Ysern, MSc.

Division of Gastrointestinal and Coagulation Drug Products

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4. **REVIEWER:** Maria Ysern, MSc.

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- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard review

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Cotherapy with human growth hormone

11. DOSAGE FORM: Powder for oral solution

12. STRENGTH/POTENCY: 5 gram packet

13. ROUTE OF ADMINISTRATION: Oral

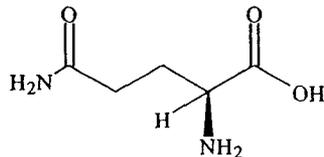
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SPOTS product – Form Completed

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16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



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Chemistry Review Data Sheet

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Microbiology	N/A		

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^b See page 13 of review notes

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EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-667

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved pending the resolution of the following issues:

- 1) Since all the information is in the related DMFs, the applicant needs to include in the NDA the Final specifications for the Drug Substance and the Drug Product.
- 2) The following changes to the label:
 - a. Under Dose and Administration: if any other beverage besides water is used, the applicant needs to provide stability data to support a 2 h storage time before use.
 - b. Under Storage and on the labels: the statement should read: "(Glutamine Powder for Oral Solution) should be stored at 25°C(77°F) with excursions allowed to 15°-30°C (59-86°F). [See USP Controlled Room Temperature]."
 - c. The sponsor should apply for an NDC number if it has not already done so.
- 3) Include a specification for reconstitution time/dissolution in the drug product specification table based on your test data.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

The information regarding the drug substance and the drug product are present in the following DMFs:

a.

b.

c.

Executive Summary Section**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Substance:**

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It will be used 6 times a day for four weeks. The treatment with Oral Glutamine should be continued to sustain the achieved increase in gut absorption and reduction of parenteral nutrition requirements.

C. Basis for Approvability or Not-Approval Recommendation

The information provided is sufficient to support the approval of this NDA.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Maria Ysern, MSc., HFD-180
ChemistryTeamLeaderName/Liang Zhou, PhD, HFD-180
ProjectManagerName/Tania Clayton

C. CC Block in DFS

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

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

/s/

Maria Ysern
4/29/04 12:04:26 PM
CHEMIST

Liang Zhou
4/29/04 01:23:24 PM
CHEMIST
Tanya: DR or Fax letter may need to be
issued to resolve minor issues.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21667/000 Sponsor: NUTRITIONAL RESTART
Code : 180 15020 SHADY GROVE RD STE 301
Priority : 1S ROCKVILLE, MD 208503364

Stamp Date : 11-AUG-2003 Brand Name : ORAL GLUTAMINE 5 GRM A PACKET
PDUFA Date : 11-JUN-2004 Estab. Name:
Action Goal : Generic Name: ORAL GLUTAMINE 5 GRM A PACKET
District Goal: 13-DEC-2003 Dosage Form: (POWDER)
Strength : 5 GRAM POWDER PACKET

FDA Contacts: T. CLAYTON Project Manager (HFD-180) 301-827-7458
 M. YSERN Review Chemist (HFD-180) 301-827-7468
 L. ZHOU Team Leader (HFD-180) 301-827-1251

Overall Recommendation: ACCEPTABLE on 18-MAR-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN
 ANDERSON PACKAGING INC
 4545 ASSEMBLY DR
 ROCKFORD, IL 61109

DMF No: AADA:

Responsibilities: _____
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER

Profile : POW OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-SEP-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : _____

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-SEP-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No:

Responsibilities:

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 18-MAR-04
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment :

[Handwritten scribble]

DMF No: AADA:

Responsibilities:

[Handwritten scribble]

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 08-SEP-03
 Decision : ACCEPTABLE
 Reason : BASED ON PROFILE

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-667

Methods Validation

The Methods Validation will be completed post approval as mentioned in the approval letter

/S/
Tanya Clayton
Regulatory Project Manager

6/9/04

APPEARS THIS WAY
ON ORIGINAL