

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-562**

**CHEMISTRY REVIEW(S)**

## MEMORANDUM

Date: March 16, 2010

To: NDA 22-562

From: Elaine Morefield, Ph.D.  
Division Director  
Pre-marketing Assessment Division II  
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-562, Carbaglu (carglumic acid) Tablets 200 mg.

Carbaglu (carglumic acid) Tablets 200 mg, is a white elongated tablet with three score marks on both sides (b) (4) engraved C's on one side. It is a dispersible tablet designed to be dispersed in (b) (4) of water and ingested or administered through a syringe via a nasogastric tube. It is indicated for treatment of acute hyperammonemia in patients with NAGS deficiency.

I have assessed the ONDQA review of NDA 22-562. I believe that there are adequate manufacturing procedures and controls for production of a quality product. The site has received an acceptable recommendation and the labeling has been acceptably revised. Therefore, I concur with the ONDQA recommendation for approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22562	----- ORIG-1	----- ORPHAN EUROPE	----- CARBAGLU (CARGLUMIC ACID)

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/s/  
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ELAINE M MOREFIELD  
03/16/2010  
Tertiary Quality Review



**Food and Drug Administration**  
Center for Drug Evaluation and Research  
Office of New Drug Quality Assessment

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**Memorandum**

**Date:** March 16, 2010  
**From:** Martin Haber, Ph.D., Review Chemist  
**Through:** Moo-Jhong Rhee, Ph.D., Branch Chief, Branch III/DP AII,  
**To:** NDA 22-562 Carbaglu Tablets  
**Subject:** Addendum to Review #1 regarding labeling and manufacturing facility inspections

Labeling and cGMP issues were outstanding at the time when CMC review #1 was completed on 2/23/2010. These issues have now been resolved.

1. Required information on labels: The applicant submitted an amendment dated 3/9/2010 containing revised draft carton and container labels.

US Distributer: The updated draft label does not specifically designate a distributor. It reads "Distributed by" followed by a blank space, and "Under license from:", "Orphan Europe SARL", "Paris, France". It looks like they will designate a distributor later after a license agreement is made by the sponsor of this NDA. Per 21 CFR 201.1(h)(5), a distributor should be designated with a qualified phrase. On March 16, 2010, the sponsor has made a commitment to add a distributor after they designate one post approval. This is deemed acceptable.

"Rx only" Statement: The required statement has been added to the carton label. The revision is acceptable.

NDC Number: The firm has requested an NDC number from the FDA and has been waiting for the number. Now the firm has made a commitment in an amendment dated 3/15/2010 that it will add the NDC number to the final carton label when it is received. This is deemed acceptable.

Bar Code: The firm has requested an exemption from the FDA for the requirement for a bar code, but the decision has not been made as of this review. However, the firm has made a commitment in an amendment dated March 15, 2010 to add the bar code to the label if the request for an exemption is denied. This is deemed acceptable.

Revised draft carton and container labels are attached (Attachment I).

2. Manufacturing cGMP requirements: On March 15, 2010 the Office of Compliance issued an overall "Acceptable" recommendation for the inspections of the manufacturing facilities. EES report is attached (Attachment II).

3. In an amendment dated 3/4/2010 additional information is provided regarding in-process controls for the synthesis of carglumic acid:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

This additional information is acceptable.

**Recommendation:**

Based on the available information on labels, the commitments made by the sponsor, and the overall “Acceptable” recommendation from the Office of Compliance, this NDA is now recommended for approval from the CMC perspective.

2 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

## Attachment II

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

<b>Application:</b>	NDA 22562/000	<b>Action Goal:</b>	
<b>Stamp Date:</b>	18-JUN-2009	<b>District Goal:</b>	19-OCT-2009
<b>Regulatory:</b>	18-DEC-2009		
<b>Applicant:</b>	ORPHAN EUROPE 9915 CAM CHIRIMOLLA SAN DIEGO, CA 92131	<b>Brand Name:</b>	CARBAGLU (CARGLUMIC ACID)
		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	
<b>Priority:</b>	1P	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
<b>Org. Code:</b>	180		001; TABLET; CARGLUMIC ACID; 200MG
<b>Application Comment:</b>	THE NDA LISTS ORPHAN EUROPE, IMMEUBLE "LE WILSON", 92058 PARIS LA DEFENSE, FRANCE, AS THE 'AUTHORIZED MANUFACTURER RESPONSIBLE FOR BATCH RELEASE FOR THE US'. THIS IS THE NDA SPONSOR. THE PRODUCT IS APPROVED FOR MARKETING IN EUROPE. (on 10-JUL-2009 by J. DAVID () 301-796-4247)		
	THE CURRENT PDUFA GOAL DATE FOR THIS NDA, NDA 22-562, IS MARCH 18, 2010. THE ORIGINAL GOAL DATE WAS EXTENDED. (on 15-MAR-2010 by M. HABER () 301-796-1675)		
	PRIORITY NDA. THE U.S. AGENT FOR THE NDA APPLICANT IS RONALD LEONARDI, PHD, TEL: 858-586-0751, FAX: 858-586-1108, EMAIL: RON@RRREGS.COM. (on 10-JUL-2009 by J. DAVID () 301-796-4247)		
	TABLET IS DISPERSED IN WATER BEFORE ORAL ADMINISTRATION. (on 10-JUL-2009 by J. DAVID () 301-796-4247)		
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	M. HABER	Review Chemist	301-796-1675
	M. KOWBLANSKY	Team Leader	301-796-1390
<b>Overall Recommendation:</b>	ACCEPTABLE	on 15-MAR-2010 by E. JOHNSON	(HFD-320) 301-796-3334

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

Estab. Comment: THIS IS THE SITE OF MANUFACTURE OF THE FINISHED PRODUCT AND BATCH TESTING OF BOTH DRUG SUBSTANCE AND DRUG PRODUCT. (on 10-JUL-2009 by J. DAVID () 301-796-4247)

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	13-JUL-2009				HABERM
SUBMITTED TO DO	13-JUL-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	16-JUL-2009	Product Specific			STOCKM
INSPECTION PERFORMED	(b) (4)		(b) (4)		CHARISSE.GREEN
<p>This inspection was conducted on behalf of (b) (4) (b) (4) of a contract drug product manufacturer; in accordance with CP 7356.002 Drug Process Inspection and CP 7346.832 Pre-Approval Inspections.</p> <p>The current inspection was an initial inspection which revealed the firm operates as a drug product manufacture. Inspectional coverage included a review of the firm's Quality, Production, Materials, Facilities &amp; Equipment, and Packaging &amp; Labeling and Laboratory Systems. Pre-Approval inspectional coverage was provided for NDA 22562/000 Carbaglu (Carglumic Acid).</p> <p>A discussion with management was held on (b) (4); an FDA 483 List of Observations was issued citing the following: the written stability program for drug products does not include reliable test methods; routine calibration of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance.</p> <p>Management promised corrections and a written response. Verbal observations were discussed with management and voluntary corrections were provided during the inspection.</p>					
DO RECOMMENDATION	15-MAR-2010			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	15-MAR-2010			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)  
 (b) (4)  
 DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 Estab. Comment: THE (b) (4) ADDRESS IS GIVEN IN THE NDA AS THE MANUFACTURER. THE NDA ALSO LISTS A SEPARATE MANUFACTURING SITE WITH THE SAME NAME. (b) (4)  
 Profile: (b) (4) (on 10-JUL-2009 by J. DAVID () 301-796-4247) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					<u>Reason</u>
SUBMITTED TO OC	13-JUL-2009				HABERM
SUBMITTED TO DO	13-JUL-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	16-JUL-2009	Product Specific			STOCKM
INSPECTION PERFORMED	(b) (4)		(b) (4)		CHARISSE.GREEN
<p>This inspection of a drug substance manufacture was conducted on behalf of (b) (4) (b) (4) in accordance with CP 7356.002F Active Pharmaceutical Ingredient Process Inspection, CP 7356.002 Drug Process Inspection, CP 7346.832 Pre-Approval Inspections and ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.</p> <p>The current inspection was an initial inspection which revealed the firm operates as a drug substance manufacture of small quantities. Inspectional coverage included a review of the firm's Quality, Production, Materials, Facilities &amp; Equipment, Packaging &amp; Labeling, and Laboratory Systems. Pre-Approval inspectional coverage was provided for NDA 22562/000 Carbaglu (Carglumic Acid).</p> <p>A discussion with management was held or (b) (4) verbal observation was discussed with management including: failure to register the facility. Management promised corrections and provided a corrective action plan for all verbal observations.</p>					
DO RECOMMENDATION	07-DEC-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	07-DEC-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22562	----- ORIG-1	----- ORPHAN EUROPE	----- CARBAGLU (CARGLUMIC ACID)

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/s/

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MARTIN T HABER  
03/16/2010

MOO JHONG RHEE  
03/16/2010  
Chief, Branch III

**NDA 22-562**

**Carbaglu  
(Carglumic Acid)  
Tablets**

**Orphan Europe, SARL**

**Martin Haber, Ph.D.  
Division of Pre-Marketing Assessment I**

**For  
Division of Gastroenterology Products**

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# Chemistry Review Data Sheet

1. NDA 22-562 (Originally NDA (b) (4), which was withdrawn)
2. REVIEW #1
3. REVIEW DATE: February 22, 2010
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NDA (b) (4) (WD by sponsor in July 2008 and not reviewed)

4/17/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

6/18/2009

Amendment

8/31/2009 (carton labels)

Amendment

2/15/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Orphan Europe, SARL; US Agent R & R Registrations  
Address: 9915 Cam. Chirimolla, San Diego, CA 92131  
Representative: Ronald Leonardi, Ph.D.  
Telephone: 858-586-0751

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Carbaglu
- b) Non-Proprietary Name (USAN, INN): Carglumic acid
- c) Code Name/# (ONDQA only): OE 312
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: In-born error of metabolism

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: 200 mg

## 13. ROUTE OF ADMINISTRATION: Oral

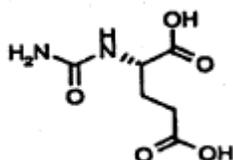
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

N-carbamoyl-L-glutamic acid; (2S)-2-(carbamoylamino)pentanedioic acid  
 $C_6H_{10}N_2O_5$



Relative molecular mass: 190.16

CAS Number: 1188-38-1 (from PharmaPendium)

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**            **No DMFs were referenced by this NDA**

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61265	Orphan Drug, clinical studies

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	Not required	2/18/2010	M. Haber
EA	Claim for categorical exclusion is granted	2/18/2010	M. Haber
Microbiology	NA		

# The Chemistry Review for NDA (b) (4)

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has submitted sufficient information to assure the identity, strength, purity, and quality for the drug product. However, while the labels have most of the required information, the final labels are pending. In addition, an overall "Acceptable" recommendation from the Office of Compliance has not been made as of this review.

Therefore, this NDA is not recommended for approval in its present form until a satisfactory recommendation is made from the Office of Compliance and acceptable revised carton and container labels are submitted.

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

NA

### II. Summary of Chemistry Assessments

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

The drug product is a 200 mg white elongated dispersible tablet with three score marks on both sides and (b) (4) engraved 'C's on one side. The drug product tablet contains 200 mg of the active ingredient, carglumic acid, with (b) (4) of excipients comprised of (b) (4) of microcrystalline cellulose (b) (4), (b) (4) of sodium lauryl sulfate (b) (4), (b) (4) of hypromellose (b) (4) of croscarmellose sodium (b) (4) silica (b) (4), and (b) (4) sodium stearyl fumarate (b) (4). All excipients are compendial grade.

A pharmaceutical development report is provided and discusses choices of excipients in order to provide for rapid disintegration and dissolution of the tablet. The report indicates that the previous formulation containing (b) (4) sodium lauryl sulfate that was used for a clinical pharmacology study shows a comparable dissolution profile to the current formulation.

The drug product is manufactured by (b) (4). During the cGMP inspection in November 2009, some deficiencies were issued via the 483 form and the Office of Compliance has been evaluating the response from the firm. The batch size is (b) (4) tablets. The process involves (b) (4)

## Executive Summary Section

(b) (4)  
(b) (4) In response to a request from the Agency, a new punch with engraved 'C's will be used for the manufacturing of the tablets for the US market.

Specification includes appearance, uniformity of dosage units, disintegration, dissolution, identification, chiral purity (b) (4), assay, impurities, (b) (4), and microbial limits. In response to a request from the Agency, the acceptance limits for chiral purity, dissolution and disintegration were tightened. The specifications for release and expiration dating period differ in regard to the acceptance limits for impurities: slightly higher acceptance limits are set for shelf-life.

There are two sizes of containers, suitable for either 5-count or 60-count tablets. The container/closure system consists of a cylindrical white polypropylene container with a large white polyethylene tamper-resistant stopper, and a silica gel desiccant. The stopper for the larger container also incorporates a clear spiral polyethylene retainer. Immediate packaging is provided by (b) (4). Specifications and diagrams are provided. Technical data and certificates of analysis for the container/closure system are provided, certifying the food contact acceptability and suitability for pharmaceutical container use.

Long term stability data at 5°C are provided for six batches of non-engraved tablets. The available stability data vary from 12 to 24 months for different batches. As requested by the Agency, the firm manufactured two batches of engraved tablets as required for US marketed products but stability data are not yet available for these batches. Stability tests include appearance, uniformity of dosage units, disintegration, dissolution, fineness of dispersion, identity, assay, (b) (4), degradation products, resistance to crushing, friability and (b) (4). Three batches after storage for 12 months at 5°C met the specification. Stability data for storage for 12 months at 25°C showed that only the (b) (4) impurity increased slightly higher under the accelerated conditions. Based on the available stability data, the proposed expiration dating period, 24 months, is granted when the tablets are stored at 5°C.

The drug substance, carglumic acid, is an allosteric activator of a critical urea cycle enzyme, carbamoyl phosphate synthetase (CPS). It is a close analog of the naturally occurring activator, N-acetyl glutamate (NAG). Carglumic acid is a urea-like derivative of the amino acid L-glutamate and contains one chiral center. The drug substance solid form is the neutral dicarboxylic acid and is a white crystalline powder. The water solubility of the drug substance depends on the (b) (4). (b) (4) polymorphic solid form has been found.

## Executive Summary Section

The drug substance is manufactured by (b) (4). The facility was found to have acceptable cGMP status during an inspection by the Agency in November 2009. The synthesis of carglumic acid consists of a (b) (4)

Regarding characterization, the drug substance structure was determined by NMR, MS, IR and (b) (4). Regarding impurities, two potential impurities are possible due to (b) (4) hydantoin-5-propionic acid (HPA) and diaza-1,3-dione-2,4-carboxy-7-cycloheptane (Diaza). Only the (b) (4) has been detected at batch release and it increases in amount during storage at elevated temperatures but not at room temperature. This impurity also increases during drug product storage at room temperature but not at refrigerated temperatures, see above discussion. The starting materials, (b) (4), were not detected in several batches and therefore routine testing is not required.

Regarding drug substance specification, identity testing is by IR and HPLC. Other tests include optical rotation, melting point, pH of 0.5% solution, loss on drying, residue on ignition, heavy metals, assay and impurities by HPLC.

Regarding chiral purity, the observed specific optical rotation is small and therefore not a very precise method for determination of chiral purity. Although a chiral HPLC method was developed, since the (b) (4) was not detected in any samples (the limit of detection was 0.1%) during the development, originally the sponsor did not propose to implement the test in the specification. However, the Agency recommended that the chiral HPLC method be included in the specification to assure chiral purity, and the sponsor agreed to do so with the limit for the (b) (4) NMT (b) (4)

Batch release data were provided that justified the proposed acceptance limits. In general, measured total impurities were low in the drug substance, about (b) (4). Appropriate in-house reference standards were established.

Stability results for 3 batches stored at 25°C/60%RH for 36 months remained within the tight specification limits. A re-test period of (b) (4) for the drug substance stored in its original packaging at room temperature is granted.

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

The drug product tablets may be dispersed in a minimum amount of water (b) (4) mL per tablet) and ingested immediately or administered through a syringe via a nasogastric tube. The suspension has a slightly acidic taste. The recommended

## Executive Summary Section

initial dose is 100 – 250 mg/kg/day. It is recommended to divide the total daily dose into two to four doses to be given before meals or feedings.

The drug product is stored refrigerated at 2 – 8 °C (36 – 46°F). After first opening of the container, it can be stored at room temperature for up to one month and kept tightly closed to protect from moisture. The expiration dating period is 24 months (2 years)

**C. Basis for Approvability or Not-Approval Recommendation**

The firm has adequately responded (2/15/2010 Amendment) to all chemistry deficiencies as described in the 1/7/2010 IR letter. Therefore, this NDA is now deemed to have provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

However, all labels do not yet have all the required information. The draft carton and container labels do not contain the “Rx only” statement, US distributor, and bar code. The labels are currently being revised. In addition, an “Acceptable” drug product manufacturing site recommendation from the Office of Compliance is still pending.

**III. Administrative****A. Reviewer’s Signature**

See DARRTS

**B. Endorsement Block**

See DARRTS

**C. CC Block**

See DARRTS

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/s/

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Martin Haber  
7/22/2009 05:00:13 PM  
CHEMIST

Moo-Jhong Rhee  
7/22/2009 05:03:08 PM  
CHEMIST  
Chief, Branch III