CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-562

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 12, 2010
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Zachary Oleszczuk, Pharm.D., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Carbaglu (Carglumic Acid) Tablets 200 mg
Application Type/Number:	NDA 022562
Applicant:	Orphan Europe, SARL
OSE RCM #:	2009-1642

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products (DGP) for evaluation of the labels and labeling of Carbaglu to identify areas that could contribute to medication errors. The Applicant submitted proposed container labels, carton and insert labeling for our review and comment.

1.2 REGULATORY HISTORY

The NDA for Carbaglu (022562) was submitted on June 17, 2009. It has orphan designation and was given a priority review with an original PDUFA date of December 18, 2009. On October 15, 2009 a major amendment was received and the goal date was extended by three months to March 18, 2010. Carbaglu received European marketing authorization in 2003.

DMEPA reviewed the container labels and carton labeling submitted August 31, 2009 (see Appendix A). Additionally, we requested and reviewed samples of the actual containers and cartons, which were submitted February 8, 2010. Our comments regarding the container labels and the carton labeling are found in Appendix B. The container label and carton labeling comments were forwarded to the Applicant via the Division on March, 2, 2010, information request letter. The Applicant provided revised container labels and carton labeling in the submission dated March 9, 2010. DMEPA comments for the container labels and carton labeling submitted on March 9, 2010, are provided in Section 3.2. DMEPA also provides comments in Section 3.1 to the Division regarding the package insert labeling and the design of the tablets, however the package insert labeling and design of the tablets are undergoing negotiations at this time and the negotiations will not be completed prior to finalizing this review.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Since Carbaglu is currently marketed in Europe, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on January 25, 2010 and February 24, 2010 to retrieve any medication errors involving risks that might relate to the product proposed in the U.S. AERS was searched using the trade name term *"Carbaglu"*, the active ingredient term *"Carglumic Acid"*, and the verbatim terms *"Carb%" and "Carg"* with the MedDRA high level group term "Medication Errors" and preferred term "Product Quality Issue".

The reports were manually reviewed to determine if medication errors occurred. Duplicate reports were grouped into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis.

The searches of the Adverse Event Reporting System did not identify any medication error reports involving Carbaglu labels, labeling, or packaging configuration. However, the lack of data does not indicate a lack of problem because medication errors are known to be underreported and Carbaglu is only marketed in foreign countries.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted March 9, 2010 (see Appendix C) and the insert labeling (no image) submitted July 30, 2009. We also reviewed samples of the tablets obtained from the Chemistry Manufacturing and Controls (CMC) review team.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations for all product labels and labeling in *Section 3.1 Comments to the Division* for discussion during the review team's label and labeling meetings. *Section 3.2 Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Nitin Patel, Project Manager, at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

A. General Comment for All Labels and Labeling

1. We defer to the Chemistry, Manufacturing, and Controls (CMC) review team for designation of the established name and dosage form of this product. It is currently presented as "carglumic acid (b) (4)" on the container labels and carton labeling and as "carglumic acid (b) (4)" and "carglumic acid (b) (4)" in the insert labeling. According to the CDER Data Standards Manual, the term (b) (4)" is no longer used for approved drug products, and has been replaced by the term "tablet, for suspension". The approved established name and dosage form, as determined by CMC, should be presented consistently across all product labels and labeling.
2. The tablets have three score marks. The Applicant has not clarified whether the tablets are intended to be broken into halves or quarters or whether the active ingredient is evenly dispersed among all of the sections. If the tablets are only intended to be broken into halves, the presence of three score marks increases the potential for medication errors because patients and healthcare practitioners may infer that the tablets should be broken at all of the score marks, resulting in quarter tablets. Addressing this issue through labels and labeling is a low leverage strategy. The optimal solution to eliminate this risk is to reformulate the tablets to include only one score mark.

B. Insert Labeling

1. Based on the dosage form (200 mg dispersible tablet) and the recommended dose range of 100 to 250 mg/kg/day, we have the following questions and comments regarding Section 2: Dosage and Administration:
    - Will the dosing allow for increments of 50 mg or 100 mg?
    - Should the product be taken with or without food?
    - Is dispersion the recommended method of administration? Can the tablets be swallowed whole or chewed? If not, what are the clinical consequences of swallowing or chewing the tablets?

- Can any liquids, other than water, be used for the dispersion? If so, what are they? Are there specific liquids that should be avoided? Is the recommended volume of 5 mL to 10 mL per tablet or per dose? Is there a maximum number of tablets that can be dispersed in 5 mL to 10 mL?
- What type of container should be used for the dispersion?

Ensure that the Dosing and Administration information is consistent between the Highlights of Prescribing Information and the Full Prescribing Information.

2. In Section 16: How Supplied/Storage and Handling, we note that the proposed product will be available in bottles of 5 and 60 tablets. Since the daily dose of Carbaglu ranges from 100 to 200 mg/kg/day, an average 60 kg adult patient will require 6000 mg per day (at the lowest dose of 100 mg/kg/day), which is equivalent to 30 tablets. The proposed package sizes of 5 and 60 tablets appear to be incongruent with this number of daily tablets. Please explain.

3.2 COMMENTS TO THE APPLICANT

Container Labels

1. To comply with 21 CFR 207.35 (b)(3)(i), ensure that the NDC number appears prominently in the top third of the principal display panel or that it appears as part of and contiguous to the bar-code symbol.
2. To comply with 21 CFR 201.25, revise the labels to include a bar code.

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

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

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/s/

ZACHARY A OLESZCZUK
03/12/2010

DENISE P TOYER
03/12/2010

CAROL A HOLQUIST
03/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Pediatric Team Labeling Review

Date: March 9, 2010 **Date Consulted:** March 3, 2010

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Gastroenterology Products (DGP)

Drug: Carbaglu® (carglumic acid) tablets, NDA 22-562

Subject: Pediatric Use Labeling

Materials Reviewed:

- Carbaglu® (carglumic acid) Tablets labeling (version edited March 3, 2010)

Consult Question: Please review the Pediatric Use subsection of Carbaglu® (carglumic acid) tablets labeling.

INTRODUCTION

Orphan Europe, S.A.R.L. submitted an original NDA (22-562) on June 17, 2009, for Carbaglu® (carglumic acid) Tablets, for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency). Orphan Drug Designation was granted for carglumic acid on January 20, 1998.

The Division of Gastroenterology Products (DGP) consulted the Pediatric Team of the Pediatric and Maternal Health Staff on March 3, 2010, to review the Pediatric Use subsection of Carbaglu® labeling.

BACKGROUND

N-acetylglutamate Synthase Deficiency (NAGS)

N-acetylglutamate Synthase Deficiency (NAGS) is a very rare hereditary urea cycle disorder that usually becomes evident in the first few days of life (although it can present later), and is associated with significant morbidity and mortality from hyperammonemia. NAGS is the rarest and most severe urea cycle disorder. The incidence of the disorder is unknown, as only a handful of cases have been reported worldwide; however, recognition of affected patients is increasing.[1] N-acetylglutamate synthase is a mitochondrial enzyme that is essential for functioning of the urea cycle. The urea cycle converts ammonia into urea in the liver, which is then eliminated through the kidneys. N-acetylglutamate synthase deficiency results in acute and chronic hyperammonemia and hyperglutaminemia, which are both very toxic to the central nervous system. Complete deficiency of N-acetylglutamate synthase is a life-threatening condition that presents soon after birth. If not immediately and sufficiently treated, this deficiency results in cerebral edema, coma, and death. Even when treated immediately, many infants are left with significant neurologic deficits.

Partial deficiency of N-acetylglutamate synthase can present with symptoms at any time in life, and symptoms are usually triggered by a stressor such as infection, trauma, or pregnancy. As with complete deficiency of N-acetylglutamate synthase, treatment must be immediate and sufficient to avoid death or significant neurologic deficits.[2]

Carglumic Acid

Carglumic acid is a synthetic structural analogue of N-acetylglutamate synthase that replaces the deficient enzyme in the urea cycle. Carglumic acid is the first specific treatment for N-acetylglutamate synthase deficiency. In patients with N-acetylglutamate synthase deficiency, carglumic acid induces rapid normalization of plasma ammonia levels, usually within 24 hours. Carglumic acid is used as adjunctive therapy in the treatment of NAGS deficiency. During acute hyperammonemic episodes concomitant administration of other ammonia lowering therapies such as ammonia scavening therapies, dietary protein restriction with hypercaloric value, and hemodialysis (in emergency situations) may be utilized.

Data on the use of carglumic acid in the treatment of NAGS comes from a retrospective review of 23 patients. Long-term data (up to 20 years) is available on 18 of these patients. All 23 patients started carglumic acid therapy in infancy or childhood, but many already had

[1] See http://emedicine medscape.com/article/941090-overview
[2] See Carglumic Acid Briefing Document for FDA Advisory Committee Meeting, January 10, 2010

neurologic deficits at the time carglumic acid was started. The data demonstrated when the treatment was initiated early (before CNS damage resulted) and maintained continuously; patients had normal growth and psychomotor development.[3]

Carglumic acid was discussed at an FDA Metabolic and Endocrine Advisory Committee Meeting on January 10, 2010, and members vote unanimously for drug approval because they felt that the reductions in ammonia were compelling, both acutely and over the long-term, and increased survival was seen over historical controls. The Committee supported carglumic acid approval despite FDA concerns with the quality and quantity of data provided to support drug approval.

The PMHS-Pediatric Team participated in a teleconference with the Sponsor on March 8, 2010, to discuss specific Carbaglu dosing and administration instructions. The Sponsor states in labeling that Carbaglu tablets must be dispersed in (b) (4) of water and taken right before feedings or meals. No rationale has been provided to date to support these specific instructions. The Sponsor will re-review the records of some of the 23 patients in the retrospective study to see if Carbaglu tablets were dispersed in other liquids or if older patients swallowed the tablets whole, rather than dispersing them first, and supply that information to DGP.

Pediatric Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

This review provides PMHS-Pediatrics' Team suggested revisions to the proposed Pediatric Use subsection of Carbaglu® (carglumic acid) Tablets labeling.

SUMBMITTED LABELING

Proposed Pediatric Use Labeling (edited March 3, 2010 version)

8 USE IN SPECIFIC POPULATIONS

(b) (4)

[redacted]

[3] See Draft Carbaglu labeling, June 17, 2010

DISCUSSION AND CONCLUSIONS

The efficacy of Carbaglu for the treatment of hyperammonemia in patients with NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began Carbaglu treatment during infancy or childhood. As this product is currently primarily used in children, information regarding safe and effective pediatric use is placed throughout labeling in the appropriate sections. All of this information does not have to be repeated again in 8.4 *Pediatric Use*.

The PMHS-Pediatric Team has concerns with dosing and administration instructions for neonates and infants. If it is determined that Carbaglu must be dispersed only in water, and not in human milk or formula, then labeling should state to use the minimum amount of water necessary for tablet dispersion for neonates and infants. Water supplementation in NAGS deficient neonates and infants may possibly lead to decreased calorie intake which could lead to a catabolic state. In addition, the extra fluid volume could lead to regurgitation of the medication and the feeding that follows.

The PMHS-Pediatric Team recommended pediatric use labeling revisions for Carbaglu® are provided below. Appendix A of this review also provides a track changes version of labeling containing our recommendations.

PMHS-PEDIATRIC TEAM LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

The efficacy of Carbaglu for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began Carbaglu treatment during infancy or childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu, however, data are limited.

Reviewer Comment: Carbaglu is currently primarily used in children and the information for safe and effective pediatric use is placed throughout labeling in the appropriate labeling sections. The use information does not have to be repeated in 8.4 Pediatric Use.

Other PMHS-Pediatric team labeling recommendations:

- Ensure that dosing and administration instructions for neonates and infants emphasize the importance for the minimum amount of water is used for Carbaglu tablet dispersion, unless the Sponsor can provide information that the tablets can be dispersed in human milk or formula.

Appendix A - PMHS-Pediatric Team Tracked-Changes Labeling Revisions

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/s/

JEANINE A BEST
03/09/2010

HARI C SACHS
03/10/2010
I agree with the labeling recommendations contained within this consult

LISA L MATHIS
03/11/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 05, 2010

TO: Donna J. Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)
Office of Drug Evaluation III

Edward D. Bashaw, Pharm.D.
Director
Division of Clinical Pharmacology III (DCPIII)
Office of Clinical Pharmacology

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 3/5/10
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: 1st Addendum to review of EIR Covering NDA 22-562 Carglumic acid tablets from Orphan Europe SARL.

At the request of DGP and DCPIII, the Division of Scientific Investigations (DSI) audited the analytical and clinical portion of a bioequivalence study (OE312/PK/99-01).

For the analytical site audit, DSI's evaluation of the Form FDA-483 items and response to the Form FDA 483 provided by (b) (4) (b) (4) and our recommendation was forwarded to DGP and DCPIII on 01/12/10. This 1st addendum evaluates the inspectional findings (Attachment 1) of the clinical site inspection conducted at SGS Aster (ASTER/CEPHAC) between 01/04-08/2010.

Study Number: ASTER/CEPHAC Reference Number, P99148 (Clinical); SPONSOR Reference Number, OE312/PK/99-01

Study Title: "Comparative Pharmacokinetic Study of OE312 in Healthy Male Volunteers after Single Oral Administration"

Clinical Site: SGS ASTER (ASTER/CEPHAC), Paris, France

OBSERVATION 1

Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent (see Attachment 1 for specific examples).

OBSERVATION 2

An adequate final report was not provided to the sponsor shortly after completion of the investigator's participation in the investigation (see Attachment 1 for specific examples).

OBSERVATION 3

An investigation was not conducted in accordance with the investigational plan (see Attachment 1 for specific examples).

Although the above Form FDA-483 observations cited documentation issues, these findings did not compromise subject safety and should not impact study outcomes. Nevertheless, the firm should take corrective action to prevent the above issues from repeating in future studies.

DSI's recommendation on the analytical site audit which was forwarded to DGP and DCPIII on 01/12/10 does not change.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Adasgupta

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI- **SGS ASTER (ASTER/CEPHAC), Paris, France**

cc: DARRTS
OND/ODE3/DGP/Griebel/Girardet
OTS/OCP/DCP3/Bashaw
OC/DSI/Salewski/Dasgupta/Yau/Rivera-Lopez

cc: email
CDER DSI PM TRACK
HFR-NE3540/ daniel.aisen@fda.hhs.gov

Draft: AD 03/03/10 03/04/10
Edits: MKY 03/03/10
DSI: 5993; O:\BE\EIRCOVER\22562.oes.car.adden1.doc
FACTS: 1077924

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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

Memorandum

Date: March 3, 2010

To: Roland Girardet, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Shefali Doshi, Regulatory Review Officer
Robert Dean, DTC Group Leader
Lisa Hubbard, Professional Group Leader
DDMAC

Subject: NDA 22-562
DDMAC labeling comments for CARBAGLU (carglumic acid) Tablets

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DDMAC has reviewed the proposed product labeling (PI) for CARBAGLU (carglumic acid) Tablets (Carbaglu) submitted for consult on August 12, 2009, and offers the following comments.

The version of the draft PI used in this review is titled, "June 2009 Carbaglu PI New Format.doc" and was accessed via the DGP eRoom on March 1, 2010. This document was last modified on February 25, 2010 at 5:57pm.

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on this proposed material.

If you have any questions regarding these comments, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

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

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/s/

KATHLEEN KLEMM
03/03/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022562

Name of Drug: Carbaglu (carglumic acid) Tablets, 200 mg

Applicant: Orphan Europe SARL, c/o U.S. Agent, R&R Registrations

Material Reviewed:

Submission Date(s): June 17, 2009

Receipt Date(s): June 18, 2009

Submission Date of Structure Product Labeling (SPL): June 17, 2009

Type of Labeling Reviewed: Word

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the sponsor's proposed package insert.

Highlights

- Add a blank line of white space between "HIGHLIGHTS OF PRESCRIBING INFORMATION" and the highlights limitation statement.
- Add white space after the DOSAGE AND ADMINSTRATION AND WARNINGS AND PRECAUTIONS SECTIONS to separate them from the subsequent sections.
- Use lower case letters for the word "TABLETS" in the Drug Name.
- Remove Registered symbol "®" from Highlights section.

- The (b) (4) section should be removed since this is not a supplement and is a first time approval.
- A pharmacologic class should be added under the INDICATIONS AND USAGE as follows: "Carbaglu (carglumic acid) is a (*insert pharmacologic class*) indicated for the….."
- The font size of the bullets under the DOSAGE AND ADMINISTRATION section should be increased from 6 point to 8 point.
- The subheadings under the WARNINGS AND PRECAUTIONS section should be in bold font and bulleted.
- The bulleted text under the WARNINGS AND PRECAUTIONS section should be justified to appear under the newly bulleted subheadings.
- The adverse reaction listed should be bulleted.
- The name and phone number of the manufacturer should be added under the ADVERSE REACTIONS" section as follows: "**To report SUSPECTED ADVERSE REACTIONS, contact (*insert company name*) at (*insert phone number*) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***".
- Since there is no proposed FDA approved patient labeling, remove "…**and FDA-approved patient labeling**" from the Patient Counseling Information Statement.

Full Prescribing Information: Contents

- Since there is only one indication, having a subsection 1.1 is not necessary.
- A solid horizontal line should be added after the Full Prescribing Information: Contents section.
- All subsection headings should be in unbolded font.

Full Prescribing Information

- Since there is only one indication, having a subsection 1.1 is not necessary.
- The Registered "®" symbol should only be used on the first use of Carbaglu and subsequent registered symbols should be removed.
- The following subheading numbers are not in bold: 5.2, 5.3, 6.1, 8.1, 8.2, 8.3, 8.4, 8.5, 12.1, 12.2, 13.1 and 16.2. Bold font should be used in all subheadings.
- The left-justification hanging indents throughout the FPI should be changed to non-hanging indents and subtext should align with the text in the section headings.
- The Absorption, Distribution, Metabolism and Elimination subheadings under section 12.2 should highlighted without using bold font. Italics can be used.
- All Cross references should be unbolded and the first letter of each word only in caps.
- The revision date at the end of the FPI should be removed.
- Manufacturer information should be included after the Patient Counseling Information.

Recommendations

The deficiencies above should be communicated to the sponsor during labeling negotiations.

Roland Girardet, M.H.S., M.S., M.B.A.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: RG/01/28/2010
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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

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/s/

ROLAND GIRARDET
02/04/2010

BRIAN K STRONGIN
02/04/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Team Review

Date: February 3, 2010 **Date Consulted:** January 8, 2010

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Gastroenterology Products (DGP)

Drug: Carbaglu® (carglumic acid) Tablets, NDA 22-562

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed:

- Pregnancy and Nursing Mothers subsections of Carbaglu® (carglumic acid) Tablets labeling dated June 16, 2009
- Draft DGP Pharmacology/Toxicology Review

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Carbaglu® (carglumic acid) Tablets labeling.

INTRODUCTION

Orphan Europe, S.A.R.L. submitted an original NDA (22-562) on June 17, 2009, for Carbaglu® (carglumic acid) Tablets, for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency). Orphan Drug Designation was granted for carglumic acid on January 20, 1998.

The Division of Gastroenterology Products (DGP) consulted the Maternal Health team (MHT) to review the Pregnancy and Nursing Mothers subsections of Carbaglu® labeling.

BACKGROUND

N-acetylglutamate Synthase Deficiency (NAGS)

N-acetylglutamate Synthase Deficiency (NAGS) is a very rare hereditary urea cycle disorder that usually becomes evident in the first few days of life (although it can present later), and is associated with significant morbidity and mortality from hyperammonemia. NAGS is the rarest and most severe urea cycle disorder. The incidence of the disorder is unknown, as only a handful of cases have been reported worldwide; however, recognition of affected patients is increasing.[1] N-acetylglutamate synthase is a mitochondrial enzyme that is essential for functioning of the urea cycle. The urea cycle converts ammonia into urea in the liver, which is then eliminated through the kidneys. N-acetylglutamate synthase deficiency results in acute and chronic hyperammonemia and hyperglutaminemia, which are both very toxic to the central nervous system. Complete deficiency of N-acetylglutamate synthase is a life-threatening condition that presents soon after birth. If not immediately and sufficiently treated, this deficiency results in cerebral edema, coma, and death. Even when treated immediately, many infants are left with significant neurologic deficits.

Partial deficiency of N-acetylglutamate synthase can present with symptoms at any time in life, and symptoms are usually triggered by a stressor such as infection, trauma, or pregnancy. As with complete deficiency of N-acetylglutamate synthase, treatment must be immediate and sufficient to avoid death or significant neurologic deficits.[2]

Carglumic Acid

Carglumic acid is a synthetic structural analogue of N-acetylglutamate synthase that replaces the deficient enzyme in the urea cycle. Carglumic acid is the first specific treatment for N-acetylglutamate synthase deficiency. In patients with N-acetylglutamate synthase deficiency, carglumic acid induces rapid normalization of plasma ammonia levels, usually within 24 hours.

Data on the use of carglumic acid in the treatment of NAGS comes from a retrospective review of 23 patients. Long-term data (up to 20 years) is available on 18 of these patients. All 23 patients started carglumic acid therapy in infancy or childhood, but many already had neurologic deficits at the time carglumic acid was started. The data demonstrated when the treatment was initiated early (before CNS damage resulted) and maintained continuously; patients had normal growth and psychomotor development.[3] Carglumic acid was discussed

[1] See http://emedicine medscape.com/article/941090-overview
[2] See Carglumic Acid Briefing Document for FDA Advisory Committee Meeting, January 10, 2010
[3] See Draft Carbaglu labeling, June 17, 2010

at an FDA Metabolic and Endocrine Advisory Committee Meeting on January 10, 2010, and members vote unanimously for drug approval because they felt that the reductions in ammonia were compelling, both acutely and over the long-term, and increased survival was seen over historical controls. The Committee supported carglumic acid approval despite FDA concerns with the quality and quantity of data provided to support drug approval.

Carglumic Acid and Pregnancy and Lactation

There are no available human data on the use of carglumic acid in pregnant or lactating women. Segment I and II studies in animals with carglumic acid at doses only slightly higher than the maximum recommended starting human dose (based on body surface area), showed no impairment in fertility; however, incomplete ossification of the supraoccipital bone occurred in fetal rats. In Segment III studies, there was a decrease in animal offspring survival at doses only slightly higher than the maximum recommended starting human dose (based on body surface area) and decreased growth in animal offspring at doses less than the maximum recommended starting human dose based on body surface area. Carglumic acid was present in rat milk, and increased mortality and decreased growth were seen in neonatal rats nursed by carglumic acid treated mothers.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. This review provides MHT's suggested revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of Carbaglu® (carglumic acid) Tablets labeling.

SUMBMITTED LABELING

(b) (4)

(b) (4)

(b) (4)

DISCUSSION AND CONCLUSIONS

As noted earlier, there are no available human data on the use of carglumic acid during pregnancy or lactation. Decreased survival and growth was seen in rat offspring from maternal carglumic acid exposure during pregnancy and lactation, at doses less than or only slightly higher than the maximum recommended human starting dose based on body surface area. Treatment with carglumic acid would be obligatory in a pregnant woman as treatment of N-acetylglutamate synthase deficiency is life-long to avoid death or significant neurologic deficits. Pregnancy would be an added stressor on a woman with N-acetylglutamate synthase deficiency, and it is unknown what effect pregnancy would have on the condition or what effect the condition would have on a developing fetus.

(b) (4)

The animal lactation data are concerning; however, due to species specific differences in lactation physiology, animal lactation data do not reliably predict drug levels in humans. In addition, the animals treated with carglumic acid did not have the enzyme deficiency that is present in humans treated with this drug. It is unclear how that difference may affect levels of drug in human serum and human milk. Taking into account the animal lactation data and the potential for the physiological stress of lactation could trigger increasing ammonia levels in a woman with N-acetylglutamate synthase deficiency, the MHT recommends against human milk-feeding when a N-acetylglutamate synthase deficient mother receives treatment with carglumic acid. As mentioned above, treatment with carglumic is life-long for NAGS, so a lactating woman does not have a choice to choose between the drug or human milk-feeding. While current labeling regulations require nursing mothers' language to either state that "caution should be exercised" of that the mother should "discontinue drug or discontinue nursing," neither of these standard statements is compatible with clinical situations that require Carbaglu treatment. Therefore, the Maternal Health Team did not include one of these statements and instead developed language specifically for this product and the situations in which it is used.

The MHT is structuring the Pregnancy and Nursing Mothers label information in a way that complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

MHT's recommended pregnancy and nursing mothers labeling revisions for Carbaglu® are provided below on pages 5-7 of this review. Appendix A of this review also provides a track

changes version of labeling and tracked changes to the DGP Pharmacology/Toxicology revisions to the Pregnancy and Nursing Mothers section of labeling. MHT met with the DGP Pharmacology/Toxicology reviewers to discuss proposed labeling revisions.

(b) (4)

(b) (4)

(b) (4)

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

Appendix A - MHT Tracked-Changes Labeling Revisions (to proposed Sponsor labeling and proposed DGP Pharmacology/Toxicology revisions)

[4] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

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/s/

JEANINE A BEST
02/03/2010

Karen B FEIBUS
02/03/2010
I agree with the content and recommendations contained in this review.

LISA L MATHIS
02/16/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 11, 2010

TO: Donna J. Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)
Office of Drug Evaluation III

Edward D. Bashaw, Pharm.D.
Division of Clinical Pharmacology III (DCPIII)
Office of Clinical Pharmacology

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 1/11/09
Acting Team Leader (Bioequivalence)
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 22-562 Carglumic acid tablets from Orphan Europe SARL.

At the request of DGP and DCPIII, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: ASTER/CEPHAC Reference Number, P99148
SPONSOR Reference Number, OE312/PK/99-01
(b) (4) Report No. 026/00029 (Analytical)

Study Title (Clinical): "Comparative Pharmacokinetic Study of OE312 in Healthy Male Volunteers after Single Oral Administration"

Study Title (Analytical): "Assays of N-Carbamyl-L-Glutamic Acid in Human Plasma and Urine Collected During a Kinetic Trial"

Please note that the audit of the clinical portion of the study was initially planned in early December, 2009 but was postponed (see details in memorandum provided in Attachment 1). The clinical site audit was conducted later at SGS Aster SAS, Paris, France between January 4-8, 2010 and Form FDA 483 was issued (Attachment 2) following the inspection. At this time, the EIR

for the clinical site inspection has not yet been received, but the ORA investigator forwarded a synopsis of the clinical inspectional findings to DSI on Jan 8, 2010 (see Attachment 3). A preliminary review of the Form FDA 483 observations and the synopsis of the inspection indicated that the findings at the clinical site are not likely to have significant impact on the study outcomes. A full and more detailed evaluation of the clinical site inspectional findings will be provided later upon receipt of the EIR at clinical site.

The audit of the analytical portion of this study was conducted at (b) (4) from November 30-December 4, 2009. Please note that assay validation and analytical runs were conducted between August 2000-August 2001 and August-September, 2000 respectively. Following the inspection, Form FDA-483 was issued (Attachment 4). (b) (4)'s response was received on 23rd December, 2009 (Attachment 5). The Form FDA-483 observations at the analytical site for study 026/00029, (b) (4) response, and DSI evaluations follow:

Analytical Site: (b) (4)

1. Failure to evaluate ion suppression by plasma components, approximately 3-fold in assays for N-carbamyl-L-glutamic acid (CGA) and approximately 8-10 fold in assays for hydantoin-5-propionic acid (HPA), and failure to evaluate variability in matrix effects on quantitation of CGA and HPA.

During audit of the source data concerning the assay validation, DSI noticed that there was variability in matrix effect on quantitation of CGA and HPA, when the analytes were extracted from matrix or mobile phase (see data in Attachment 6). (b) (4) did not conduct additional experiments to address the variability in matrix effect in their written response to the Form FDA-483. Therefore, the accuracy of the determination of the analytes in subject plasma cannot be confirmed. (b) (4) argues that matrix effect is likely to affect samples and periods in a balanced way but (b) (4) did not submit data to support their claim. Thus, the within-batch variability of matrix effect could not be assessed from the data presented during the audit.

2. Failure to accurately report all validation experiments conducted in the method validation for N-carbamyl-L-glutamic acid (CGA) and hydantoin-5-propionic acid (HPA). For example:

a. Failure to report all validation experiments containing valid data. For example, data from three experiments for intra run precision and accuracy at LLOQ were discarded and not reported because the data failed to meet acceptance criteria.

The source data revealed that results for the experiment on precision and accuracy at LLOQ were only from one passing experiment. The data from three experiments with failing precision and accuracy results were not reported. This practice is objectionable as it introduces bias in the results.

(b) (4) acknowledged the 483 observation and said that data from failing runs are currently included in their reports.

b. Failure to accurately report the dilution test experiment conducted during pre-study method validation.

The results for dilution testing were not from a single experiment, but from two separate experiments. Failing data from each experiment were not reported. Instead, passing data from the two experiments were reported as one experiment. (b) (4) acknowledged the observation. In their response, the firm said that all runs are currently included in their reports.

c. Inter run precision and accuracy at LLOQ was not accurately reported for CGA as the reported data excluded outliers.

Not all method validation data were included in the statistical analysis. During the inspection, (b) (4) was asked to recalculate inter run precision and accuracy at LLOQ for CGA. When all data were included, the precision results failed to meet the acceptance criteria (≤ 20% CV).

3. Failure to reject analytical runs where less than (calibrators failed to meet the acceptance criteria. For example analytical runs with batch ID 000824D and 000808V for HPA analysis were accepted when the required (b) (4) failed to meet the acceptance criteria.

Although the above observations represent violation of the study plan, this finding should not impact study integrity as HPA concentrations were not used in bioequivalence determination. Nevertheless, the firm should assure that this condition is not repeated for future studies.

4. Processed sample storage stability at 4 degrees C was not demonstrated for N-carbamyl-L-glutamic acid (CGA) and hydantoin-5-propionic acid (HPA) during method validation. For study 026/00 029, some of the processed samples were stored in the autosampler for up to 3 days before injection.

In their written response, (b) (4) said that they conducted a new processed stability experiment and provided data showing that stability in the auto-sampler was stable for up to 72 hours. (Attachment 5 page 11).

5. Stability at room temperature was not demonstrated during method validation. The time durations while plasma samples were held at room temperature during processing were not recorded.

In their written response, (b) (4) presented stability data to show that CGA and HPA were stable in plasma over a period of 22 hrs (Attachment 5, page 8).

6. Validation of assay selectivity is inadequate. Only three blank plasma matrices were evaluated instead of at least six during method validation.

(b) (4) acknowledged this finding but stated in their written response that they currently evaluate selectivity from six independent sources of matrix (Attachment 5, page 13).

7. QC concentrations were not representative of the actual subject sample concentrations of CGA. The median Cmax values for treatment A and B was 2880 and 2550 (individual Cmax values ranged from 1850 ng/mL to 4800 ng/mL) respectively. QC levels for CGA were 150, 5000, and 8000 ng/mL.

Thus only two QC concentrations were representative of study samples. For future studies, the firm agreed to select QC sample concentrations that are representative of study samples.

8. Failure to select chromatography integration parameters using objective criteria.

During the study period, the site had no established procedures and criteria for selection of integration parameters. In the absence of established procedures, and in the absence of an audit trail, it could not be confirmed that selection or changes to automatic integration parameters did not bias run acceptance.

(b) (4) acknowledged the findings in their response but stated that an SOP for selection of integration parameters was implemented on April 7, 2005 (Attachment 5, page 20).

9. Several chromatograms, including calibrators and QCs, were reintegrated without documenting the reasons and without retaining the original records.

Although electronic records were not available, the paper records revealed that numerous chromatograms were manually reintegrated. In many runs, QCs and standards were modified, potentially affecting run acceptance (see Exhibit 1). As the original chromatograms with automatic integration were not maintained and could not be provided during the inspection, it could not be confirmed that manual change was warranted

In their response (Attachment 5, page 4), (b) (4) acknowledged that reasons for reintegrations were not recorded at the time of the study. The firm's current SOP requires the documentation for reintegration. Note that in their written response, (b) (4) claims that the original chromatograms were available during inspection. This, in fact, is incorrect as the original chromatograms were not made available when requested by DSI during the inspection.

10. Failure to document all aspects of study conduct. Specifically:

a) There is no documentation on the sources of matrix (blank plasma or urine) used to prepare the QCs and calibrator.

b) Freezer log book did not capture the time when samples (QCs and subject samples) were taken out or put back into the freezer.

c) Weighing of the reference standards was not verified by countersignature when balance print outs were not available.

d) Failure to maintain sufficient written records for all equipment inspection, maintenance, testing, calibrating and/or standardizing operations.

e) There was no documentation to confirm that the auto sampler injection sequences from analytical runs were verified in study 026/00 029.

(b) (4) acknowledged the findings. They stated that they would implement corrective measures to address the deficiencies in observations 10a, b and c. In response to observation 10d, the firm reiterated their intention to document all events and activities. In response to observation 10e, the firm claimed that analysts now check vial positions after loading the autosampler.

11. Failure to implement SOP for incurred sample reproducibility experiment.

The firm is currently drafting an SOP for incurred sample reproducibility.

Conclusion:

Following the above inspection, DSI concludes that the accuracy of pharmacokinetic measurements in study 026/00029 is not assured because of deficiencies in pre-study assay validation, analytical runs, (see 483 Item 2, 7, 8, 9, and 10 and variation of matrix effect as cited in 483 Item 1.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI- (b) (4)

cc: DARRTS
OND/ODE3/DGP/Griebel/Girardet
OTS/OCP/DCP3/Bashaw
OC/DSI/Salewski/Dasgupta/Yau/Rivera-Lopez

cc: email
CDER DSI PM TRACK
HFR-NE3540/ daniel.aisen@fda.hhs.gov

Draft: AD 01/05/10
Edits: MFS 01/05/10, MKY 1/10/10
(b) (4); O:\BE\EIRCOVER\22562.oes.car.doc
(b) (4)

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

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/s/

ARINDAM DASGUPTA
01/12/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 12/2/2009

TO: Roland Girardet, Regulatory Project Manager
Helen Sile, Medical Officer
Division of Gastrointestinal Products

FROM: Khairy Malek, Medical Officer
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: # 22-562

APPLICANT: Orphan Europe, SARL

DRUG: Carbaglu (carglumic acid)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Treatment of hyperammonemia due to the deficiency of the hepatic Enzyme N-acetylglutamate synthase (NAGS)

CONSULTATION REQUEST DATE: 7/14/2009

DIVISION ACTION GOAL DATE: 12/18/09

PDUFA DATE: 12/18/09

1. BACKGROUND:

Enzyme N-acetylglutamate synthase (NAGS) deficiency is a recessive hereditary urea cycle disorder which causes hyperammonemia. Acute and chronic hyperammonemia is toxic to the nervous system and can lead to cerebral edema, coma and eventually death. For those who survive the acute episode, psychomotor retardation is the frequent outcome.

The data submitted in support of this NDA is comprised solely of a retrospective collection of medical record data obtained from patients treated with this condition. A controlled clinical trial in NAGS deficiency patients could not be conducted because the disease has an extremely low incidence, can be life threatening, and is severely symptomatic. This NDA presents the information collected retrospectively on confirmed NAGS deficiency patients who received chronic treatment with carglumic acid. There was no protocol and the analysis is based on data collected from 1991 to December 2007 on few patients.

The primary objective was to review the clinical and biological response of NAGS deficiency patients to carglumic acid within the first 7 days of treatment (short-term outcome) and at the last report (long-term outcome). The primary biomarker for the short-term analysis was ammonemia, supported by glutaminemia and citrullinemia. For the long-term analysis, all 3 biomarkers (ammonemia, glutaminemia and citrullinemia were considered equally.

Two clinical sites were inspected in support of this NDA. The French site, with a large number (6) of subjects and superior documentation and one additional site in Germany were chosen for inspection. Subjects from additional sites in England and Sweden were also included in the cases presented to the review division for a total of 20 patient cases submitted in the NDA.

II. RESULTS (by Site):

Name of CI, Location	**# of Subjects:**	**Inspection Date**	**Final Classification**
Nathalie Guffon, M.D. Centre de reference des maladies metaboliques, 59 Boulevard Pinel, 69677, Bron Cedex, France	6 Subjects	November 9-13, 2009	N/A This is a retrospective collection of data from the medical records of patients with this rare hereditary disease. Therefore, this inspection was conducted as a investigation for data verification rather than a full GCP inspection and a final classification will not be assigned for this

			investigation.
Peter Gessler, M.D. Klinik fur Kinder und Jugendliche D-78461 Konstanz, Germany	2 Subjects	November 23-26, 2009	N/A Same as above

Key to Classifications
NAI = No deviation from regulations.
VAI = 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.

Note: The findings described below are based on personal participation of DSI reviewer, Dr. Malek, in the inspections.

1. Name of CI: Nathalie Guffon, M.D.
   Centre de reference des maladies metaboliques, 59 Boulevard Pinel, 69677, Bron Cedex, France

   a. What was inspected: The field investigator and DSI reviewer reviewed all the medical records and supporting documents of the 6 subjects in the study. The records included: hospital records, data listings, individual patient narratives and laboratory reports from birth or shortly after until 2007 (as reported in the NDA) for all of the subjects. Source documents for the period between 2007 and December, 2009 were also reviewed at the request of the review division to assess survival status of subjects beyond data reported in the NDA for 5 of 6 subjects (one subject the latest record was from 2008)..

   b. General observations/commentary: At this site, the hospital records and lab reports were well preserved and documented. The data listings provided in the NDA were supported by the records at the site. The efficacy parameters were clearly verified and the adverse reactions were adequately reported. There was a minor inaccurate record in that Subject #13 (b) (6) had a decompensation episode in November 2001 when the plasma ammonia increased to 175 umol/L. The reason given in the narrative was that the subject did not take the carglumic acid for 48 hours. The CI wrote in the hospital record that the subject took the drug with "Coca Cola" which in her opinion inactivated the drug. When the DSI reviewer asked the Medical Director of the company who attended the inspection in Konstanz, he said that the company sent some "Query Forms" to the CI on 11/12/2008 asking for an explanation regarding the high ammonia level on November 11, 2001. The CI wrote as a reply to the inquiry "Last intake of carglumic acid 48 h ago. Blood samples taken on November 13 NH3 = 22 umol/L". I kept a copy of the reply.

   c. Assessment of data integrity: The data from this site are reliable and can be used in

support of the NDA

2. Peter Gessler, M.D.
   Klinik fur Kinder und Jugendliche, D-78461 Konstanz, Germany

   a. What was inspected: The field investigator and DSI medical officer reviewed all the medical records and supporting documents including the hospital records, lab reports, and patient narratives. At this site, there were only 2 subjects, #5 and #6. Patient #5 is homozygous for NAGS deficiency and is currently continuing on treatment with carglumic acid, while subject #6 was discontinued from using carglumic acid in September 2003 after a DNA test confirmed heterozygosity for NAGS deficiency. The CI told the DSI reviewer that the subject is not currently followed in the clinic; however, he has been instructed to come to the clinic if he suffers an infection or any symptoms.

   b. General observations/commentary: This site is different from Dr. Guffon's site. At this site, at least 6 CIs took care of the patients since 1995; all are retired or have left the hospital except one. They were not specialized in metabolic diseases like Dr. Guffon and some of them used to send the cases to other specialists for advice. For both subjects, part of the hospital records are missing: For subject #5, hospital records from (b) (6), from (b) (6), and from (b) (6) are missing. For Subject #6, there were no hospital records from (b) (6), no records from (b) (6), and no records after (b) (6) (this subject was found to be heterozygous in 2003). The sponsor told the DSI medical officer that lack of availability of some of the records for inspection was because some of the records were sent to other specialists for advice. In spite of this lack of availability for review of all records during the inspection, the inspection was able to verify all the data listings presented to the FDA through the lab reports and other documents. The 2 subjects at this site are currently alive and well. The current CI, Dr. Gessler is specialized in metabolic diseases; however, he only recently assumed responsibility for these patients.

   c. Assessment of data integrity: The data from this site are reliable and could be verified and can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This NDA is comprised of data solely obtained from retrospective review of medical records from patients treated with carglumic acid for enzyme N-acetylglutamate synthase (NAGS) deficiency. Two clinical sites were evaluated and records reviewed in support of this application. The data submitted in the application was verified to be accurate in comparison to source documents reviewed at the clinical sites. The data generated from these 2 sites are reliable and can be used in support of the NDA.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

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/s/

JEAN M MULINDE
12/04/2009
Dr. Malek is the primary author of document, I have entered document into DARRTS for Dr. Malek. In addition, as Acting Branch Chief for GCP2, I am signing document for Tejashri Purohit-Sheth, M.D.

KHAIRY W MALEK
12/04/2009

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 16, 2009.

TO: Donna J. Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)
Office of Drug Evaluation III

Dennis Bashaw, Pharm.D.
Director
Division of Clinical Pharmacology III (DCPIII)
Office of Drug Evaluation III

FROM: Arindam Dasgupta Ph.D.
Staff Fellow (Bioequivalence)
Division of Scientific Investigations (DSI)

THROUGH: C.T. Viswanathan, Ph.D. Mani K. Yan 11/16/09
Associate Director (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Inspection of clinical facility, Aster-Cephac, for Carbaglu bioequivalence study conducted under NDA 22562

This memorandum is to inform DGP and DCPIII that DSI inspection of the above facility was originally scheduled on December 7-11, 2009. However, DSI was informed by the study sponsor and the study site that their facility was not ready for FDA inspection due to reasons stated in Attachment 1. Thereafter, DSI informed the sponsor that the inspection could not be delayed due to review timelines (Attachment 2). Yet, steps were not taken by the sponsor to facilitate the inspection as originally scheduled. Recently, DSI was informed that the earliest time for inspection at Aster-Cephac would be January 4-8, 2010. In light of the delay, DSI has requested the ORA investigator conducting the clinical site inspection to forward us the inspectional findings as soon as possible, following the inspection in early January, 2010.

Please note that the analytical site inspection at (b) (4) (b) (4) will be conducted on November 30-

December 4, 2009 as originally scheduled.

Arindam Dasgupta, Ph.D.
Staff Fellow

Attachments

1. Letter from Clinical Site
2. Correspondences

cc: DARRTS
OND/ODE3/DGP/Griebel/Girardet
OTS/OCP/DCP3/Bashaw
OC/DSI/Viswanathan/Yau/Dasgupta

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

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/s/

ARINDAM DASGUPTA
11/16/2009

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: **August 31, 2009**

To: **Donna Griebel, M.D., Director**
Division of Gastroenterology Products

Through: **Michael Klein, Ph.D., Director**
Lori a. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: **JianPing (John) Gong, M.D., Ph.D., Medical Officer**
Controlled Substance Staff

Subject: **Consultation on Carbaglu (Carglumic acid) Tablets**

NDA #:	**22562**
Document date:	**June 17, 2009**
Indication:	**NAGS (N-acetylglutamate synthase) deficiency**
Strengths:	**200 mg**
Sponsor:	**ORPHAN Europe SARL**

Submission: NDA 22562 was submitted as paper copy. CSS received documents of Module 4: 1.1-1.13 and reviewed the following document from the NDA:

- Behavioral Irwin Test and effect on body temperature following single oral administration in rats of both sexes.

Background

The Division of Gastroenterology Products (DGP) consulted the Controlled Substance Staff (CSS) regarding the abuse potential of Carbaglu (carglumic acid) Tablets for oral administration. Specifically, DGP asked CSS to determine whether the Sponsor needs to address the abuse potential of Carbaglu.

NAGS is a mitochondrial enzyme, which is essential for the function of the urea cycle converting ammonia into urea in the liver cell. NAGS deficiency, the most severe among Urea Cycle Disorders (UCD) is a very rare autosomal genetic disease presenting with extremely high plasma levels of ammonia, which leads to permanent and irreversible damage of the central nervous system. It is a serious life-threatening clinical condition. The symptoms start shortly after birth, rapidly leading to cerebral edema, coma and eventually death without appropriate treatment. Children born with this genetic disorder

often die before diagnosis due to the severity and fast deterioration of clinical status. The incidence of UCD is 1 in 30,000 births, and NAGS deficiency is the rarest among the UCD.

Carbaglu (Carglumic acid, N-carbamyl-L-glutamic acid) is a synthetic amino acid analogue of the physiological activator (N-acetyl glutamate) of the first enzyme of the urea cycle, carbamoyl phosphate synthetase I (CPS I). It exhibits therefore its pharmacological effect by activation of CPS I.

CSS Responses

The Sponsor didn't ask specific question for CSS to address.

In the documents we received, data of the Irwin Test are the only behavioral information the Sponsor submitted. Carbaglu had no statistically significant neurobehavioral, neurovegetative, neurotoxic or psychotropic effects and had no effect on body temperature in the rat. Based on the limited data submitted, our primary conclusion is that there is no obvious evidence to indicate abuse potential of Carbaglu.

Summary of Submitted Materials

Animal Study

Behavioral Irwin test and effects on body temperature following single oral administration in rats of both sexes.

Purpose

To evaluate any possible neurobehavioral, neurovegetative, psychotropic or neurotoxic effects of N-carbamyl-L-glutamic acid and its effect on body temperature following single oral administration in rats of both sexes.

Study design

The study involved 5 groups of 4 male and 4 female Sprague-Dawley rats weighing between 150g and 187g.

Groups were as follows:

- Group 1: control group dosed with the vehicle of N-carbamyl-L-glutamic acid (1% carboxymethylcellulose hydrogel),
- Group 2: method-control group dosed with a method-control substance, clonidine, at a dose of 3 mg/kg,
- Group 3: group dosed with N-carbamyl-L-glutamic acid at a dose of 250 mg/kg,
- Group 4: group dosed with N-carbamyl-L-glutamic acid at a dose of 500 mg/kg,
- Group 5: group dosed with N-carbamyl-L-glutamic acid at a dose of 1000 mg/kg.

On the study day, animals were first scored by the IRWIN standardized observation battery and the body temperature was measured. Subsequently, they were dosed orally with N-carbamyl-L-glutamic acid, its vehicle or clonidine, in a volume of 10 ml/kg. The IRWIN scores as well as measurement of body temperature were performed again at 60, 120, 180, 240, 360 minutes and 24 hours after administration.

Results

Under the experimental conditions adopted, N-carbamyl-L-glutamic acid administered orally at a does of 250, 500, 1000 mg/kg had no statistically significant neurobehavioral, neurovegetative, neurotoxic or psychotropic effects and had no effect on body temperature in the rat of either sex.

Under the same conditions, the method-control substance (clonidine, 3 mg/kg, p.o.) induced, as expected, its typical sedative and neurovegetative effects as well as an hypothermic effect, showing the validity of the method used.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22562	ORIG 1	ORPHAN EUROPE	CARBAGLU (CARGLUMIC ACID)

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/s/

Jianping P GONG
08/31/2009

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MICHAEL KLEIN
08/31/2009