

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-562**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022562

SUPPL # 0000

HFD # 180

Trade Name Carbaglu

Generic Name Carglumic acid

Applicant Name Orphan Europe S.A.R.L.

Approval Date, If Known March 18, 2010

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====  
Name of person completing form: Lynne Yao, M.D.  
Title: Acting Medical Officer Team Leader  
Date: March 10, 2010

Name of Office/Division Director signing form:  
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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

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/s/

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ROLAND GIRARDET  
03/16/2010

DONNA J GRIEBEL  
03/16/2010

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22562 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Division of Gastroenterology Products PDUFA Goal Date: 03/18/2010 Stamp Date: 6/18/2009

Proprietary Name: Carbaglu

Established/Generic Name: carglumic acid

Dosage Form: tablet

Applicant/Sponsor: Orphan Europe S.A.R.L. c/o U.S. Agent, R&R Registrations

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
  - (2) \_\_\_\_\_
  - (3) \_\_\_\_\_
  - (4) \_\_\_\_\_
- 

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency).

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?  
 Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?  
 Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the*

pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_

**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)  
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
---

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:  
 Disease/condition does not exist in children  
 Too few children with disease/condition to study  
 Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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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ROLAND GIRARDET  
03/10/2010

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Wednesday, March 17, 2010 12:36 PM  
**To:** R & R Registrations  
**Cc:** 'jennifer Spinella'; 'ann@rrregs.com'  
**Subject:** NDA 022562: Carbaglu PMR Dates

Dear Dr. Leonardi,

In reference to the Final Protocol Submission date of December 31, 2010, which you proposed in your March 15, 2010 communication regarding the Post-Marketing Requirement (PMR) to conduct a 2-Year carcinogenicity study in a single species, we have the following recommendation:

We strongly recommend that you submit your proposed study protocol for a Special Protocol Assessment (SPA). The Executive Carcinogenicity Assessment Committee will review your protocol and provide recommendations within 45 days of receipt of your study protocol. Therefore, in order to allow sufficient time for review of your protocol, we recommend a Final Protocol Submission date of February 28, 2011.

Please refer to the following guidances regarding the submission of Carcinogenicity study protocols:

ICH Guidances

S1B Testing for Carcinogenicity of Pharmaceuticals  
S1C(R2) Dose Selection for Carcinogenicity Studies

FDA Guidances

Carcinogenicity Study Protocol Submissions  
Special Protocol Assessment

Further, we recommend a Final Report Date of September 20, 2014 in order to allow sufficient time to draft the final report.

If you have any questions, please feel free to contact me at your earliest convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA*  
*Regulatory Project Manager*  
*Division of Gastroenterology Products*  
*Office of Drug Evaluation III*  
*Center for Drug Evaluation and Research*  
*U.S. Food and Drug Administration*  
*10903 New Hampshire Ave.*  
*Silver Spring, MD 20993-0002*  
*Phone: (301) 796-3827*  
*Email: roland.girardet@fda.hhs.gov*

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

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

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/s/

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ROLAND GIRARDET  
03/17/2010



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

*If not a PMR, skip to 4.*

- **Which regulation?**

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

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

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

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

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

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

The Applicant will conduct a 2-year carcinogenicity study in a single species as a post-marketing requirement study.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

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

Agreed upon:

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

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

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

**PMR/PMC Development Coordinator:**

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

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(signature line for BLAs)



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

The patient registry will provide prospectively obtained, long-term dietary protein management, clinical status, neurocognitive, psychomotor, growth and development data that are currently lacking and will provide new long-term safety information.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

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

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

The study is a prospective registry study that will obtain long-term clinical safety information. Data to be collected will include patient demographics, details of treatment with carglumic acid, other therapies for hyperammonemia and dietary protein management, clinical status, neurocognitive and psychomotor status, growth and development status, and adverse events.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

*Continuation of Question 4*

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

Agreed upon:

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

1604-2

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

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

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**PMR/PMC Development Coordinator:**

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

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

*If not a PMR, skip to 4.*

- **Which regulation?**

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

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

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

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

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

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

This study will be performed as a sub-study within the registry for all patients with NAGS deficiency that will collect information on pregnancy and fetal outcomes.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

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

Agreed upon:

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

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

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

**PMR/PMC Development Coordinator:**

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

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(signature line for BLAs)



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

*If not a PMR, skip to 4.*

- **Which regulation?**

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

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

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

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

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

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

This will be an in vitro study to determine the CYP enzymes mediating the metabolism of carglumic acid and their relative contributions as part of the assessment of drug interaction potential for Carbaglu. The Sponsor is currently conducting a study entitled “*In vitro* metabolic stability of N-carbamyl [14C]-glutamic acid in rat, mini-pig, dog, monkey and human hepatocytes”. The study report should include documentation of the viability of the hepatocytes for various cytochrome P450 enzymes.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

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

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)
- 
- Other  
 Complete and submit the final study report for the on-going study entitled, “*In vitro* metabolic stability of N-carbamyl [<sup>14</sup>C]-glutamic acid in rat, mini-pig, dog, monkey and human hepatocytes”. The study report should include documentation of the viability of the hepatocytes for various cytochrome P450 enzymes.
- 

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

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

**PMR/PMC Development Coordinator:**

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

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(signature line for BLAs)



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

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- **Which regulation?**

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

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

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

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

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

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

This will be an *in vitro* drug interaction study to identify the potential for carglumic acid to inhibit or induce Cytochrome P450 enzymes. This study will be a post-marketing commitment.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

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

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)
- 
- Other  
 The study will be an *in vitro* study to assess the potential for carglumic acid to inhibit or induce the Cytochrome P450 enzymes.
- 

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

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

**PMR/PMC Development Coordinator:**

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

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(signature line for BLAs)

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

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

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/s/

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ROLAND GIRARDET  
03/17/2010

LYNNE P YAO  
03/17/2010

## Girardet, Roland

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**From:** Girardet, Roland  
**Sent:** Tuesday, March 16, 2010 2:22 PM  
**To:** R & R Registrations  
**Cc:** 'jennifer Spinella'; 'ann@rrregs.com'  
**Subject:** NDA 22562: Carbaglu distributor information

Dear Dr. Leonardi,

21 CFR 201.1(h)(5) is the regulation that describes how the distributor information must be presented on the label.

Per our conversation, please submit to the NDA a correspondence committing to add distributor information to the carton and container labeling for Carbaglu. There is a very specific format in which the information must be displayed so when you submit the commitment, please make sure to state that the information will be presented as described in the regulation noted above.

Thanks,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: [roland.girardet@fda.hhs.gov](mailto:roland.girardet@fda.hhs.gov)*

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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ROLAND GIRARDET  
03/16/2010

# MEMORANDUM OF TELECON

DATE: 03/15/2010

APPLICATION NUMBER: NDA 022562

**BETWEEN:**

Name: Jennifer Spinella, R&R Registrations  
Phone: 858-586-0751  
Representing: Orphan Europe

**AND**

Name: Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager  
Division of Gastroenterology Products (DGP), HFD-180

**SUBJECT:** Bar codes and NDC numbers on labeling

**Background:**

On March 2, 2010, an information request was sent to Orphan Europe requesting numerous revisions to their carton and container labeling. Among the items requested were the need for an NDC number and a bar code. On March 9, 2010, Orphan Europe submitted revised carton and container labeling, which did not address these two requested items. The purpose of this call was to make the applicant aware that these items were still outstanding and to obtain a commitment to make these revisions to the labeling.

**Discussion:**

Orphan Europe acknowledged the fact that the NDC number and the bar code were still missing. They stated that a request for an NDC labeler code had been submitted to the FDA on March 8, 2010, but that a response was still pending and that a request for an exemption to the bar code rule had also been submitted to the FDA. The FDA asked Orphan Europe to submit to the NDA a correspondence indicating their agreement to add the NDC number to the carton and container and package insert labeling and also committing to add the bar code to the carton and container labeling if the request for exemption was denied.

The applicant agreed to submit the correspondence making these commitments.

The call ended.

Roland Girardet  
Regulatory Project Manager

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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ROLAND GIRARDET  
03/16/2010

## Girardet, Roland

---

**From:** Girardet, Roland  
**Sent:** Monday, March 15, 2010 5:56 PM  
**To:** 'jennifer Spinella'  
**Cc:** R & R Registrations; 'ann@rrregs.com'  
**Subject:** NDA 022562: Revised Package Insert  
**Attachments:** Carbaglu PI 03\_15\_2010.doc

Dear Dr. Leonardi,

Attached please find the revised Carbaglu package insert with an updated to the Dosage and Administration section.

Please submit a response indicating agreement to the changes by Tuesday, March 16, 2010.

If you have any questions, please feel free to contact me at your earliest convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

7 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)

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/s/

ROLAND GIRARDET  
03/15/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): Jeanine Best, Pediatric and Maternal Health Staff

FROM (Name, Office/Division, and Phone Number of Requestor): Roland Girardet/Regulatory Project Manager/Division of Gastroenterology Products (DGP)/ 301-796-3827

DATE  
03/03/10

IND NO.

NDA NO.  
22562

TYPE OF DOCUMENT  
Package Insert

DATE OF DOCUMENT  
03/03/2010

NAME OF DRUG  
Carbaglu (carglumic acid)  
Tablets, 200 mg

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
03/10/10

NAME OF FIRM: Orphan Europe SARL

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input checked="" type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DGP requests PMHS (Jeanine Best) assistance in reviewing the Pediatric Section of the Carbaglu (carglumic acid) tablets Package Insert, currently being reviewed under NDA 22562.

The label is in the eRoom at the following link:[http://erom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0\\_b53a](http://erom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_b53a)

I

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



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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ROLAND GIRARDET  
03/03/2010



NDA 22562

**INFORMATION REQUEST**

Orphan Europe SARL  
c/o R&R Registrations  
Attention: Ronald Leonardi, Ph.D.  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbaglu (carglumic acid) Tablets, 200 mg.

We also refer to your August 31, 2009 and February 12, 2010 submissions, containing proposed carton and container labeling.

We are reviewing these submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Carton Labeling**

1. Delete the box containing the graphic which appears on the principal display panel and on the top flap. The graphic is distracting and provides no useful information to healthcare practitioners or patients and may lead to confusion, especially with the number 5. This number may be misinterpreted as a strength or number of tablets to administer. Alternatively, you may include an actual image or photograph of the tablet.
2. To comply with CFR 201.10(a), delete the dark yellow line separating the proprietary name and strength from the other product information. As currently presented, the line is considered intervening matter.
3. Relocate the established name (carglumic acid) so that it appears immediately beneath the proprietary name. Relocate the dosage form so that it follows the established name. Relocate the product strength (200 mg) so that it appears immediately beneath the established name and dosage form. Revise to read as follows:  
Carbaglu  
(carglumic acid) Tablet  
200 mg
4. Ensure that the net quantity statement is presented with less prominence than the product strength.

5. 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.
6. To comply with 21 CFR 201.25, revise the labeling to include a bar code.
7. Add the “Rx only” statement to the principal display panel.
8. Relocate the expiration date, lot number, and date of first opening from the bottom flap to the side panel, to increase its prominence.
9. Add “Discard one month after first opening” statement near the “Date of first opening” field.
10. Clarify the storage instructions to read as follows:
  - Before opening, store refrigerated at 2°-8° C (26°-46° F)
  - After first opening of the container:
    - Write the date of first opening on the (b) (4) container.
    - Discard one month after first opening.
    - Do not refrigerate after opening
    - Do not store above 30° C (86° F).
    - Keep the container tightly closed in order to protect from moisture.
    - Do not use after the expiration date stated on the carton and container.
11. Revise the distributor statement to read “Distributed by\_\_\_“ or an appropriate phrase, to comply with 21 CFR 201.1(h)(5).

## Container Labels

1. We note that the container labels peel back to reveal information underneath. Peel-off labels can often be torn and important information may be lost. Revise to include all information on a standard container label.
2. Delete the graphic which appears on the principal display panel. The graphic is distracting and provides no useful information to healthcare practitioners or patients and may lead to confusion, especially with the number 5. This number may be misinterpreted as a strength or number of tablets to administer. Alternatively, you may include an actual image or photograph of the tablet.
3. Relocate the established name (carglumic acid) so that it appears immediately beneath the proprietary name. Relocate the dosage form (tablets) so that it follows the established name. Relocate the product strength (200 mg) so that it appears immediately beneath the established name and dosage form. Revise to read as follows:

Carbaglu  
(carglumic acid) Tablet  
200 mg

4. Increase the prominence of the proprietary and established names and the product strength by increasing the font size and weight.
5. Revise the net quantity statement to read as follows:  
5 tablets per container  
or  
60 tablets per container  
Ensure that the net quantity statement is presented with less prominence than the product strength.
6. 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.
7. To comply with 21 CFR 201.25, revise the labels to include a bar code.
8. Add the “Rx only” statement to the principal display panel if space permits.
9. Relocate the expiration date, lot number, and discard instructions from the base to a side panel. Add a “Date of first opening” blank field near the “Discard one month after first opening” statement.
10. Revise the storage instructions (as outlined above in the Carton Labeling section) and present the information on a side panel.
11. Revise the distributor statement to read “Distributed by\_\_\_“ or an appropriate phrase, to comply with 21 CFR 201.1(h)(5).
12. Delete the word (b) (4) before tablets.
13. The storage statement instructions should be added to the container label and be consistent with carton labeling.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/

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BRIAN K STRONGIN  
03/02/2010

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Friday, February 19, 2010 1:39 PM  
**To:** 'ann@rrregs.com'  
**Cc:** 'Ron G. Leonardi'; 'jennifer Spinella'  
**Subject:** Draft Carbaglu Package Insert  
**Attachments:** Draft Carbaglu PI Feb\_19\_10 (clean).doc; Draft Carbaglu PI Feb\_19\_10 (with comments).pdf

Dear Ann,

Attached, please find the Carbaglu package insert (PI) incorporating the Division's proposed revisions thus far. I have included a clean Word copy as well as a pdf with specific comments for Orphan Europe. As I mentioned in my last email, we hope to discuss these revisions as part of next week's teleconference. Please keep in mind that some additional revisions will likely be forthcoming as we continue to review the package insert.

If you have any questions, please feel free to contact me at your earliest convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

14 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)

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/s/  
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ROLAND GIRARDET  
02/19/2010

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Tuesday, February 09, 2010 12:15 PM  
**To:** 'Ron G. Leonardi'  
**Cc:** 'ann@rrregs.com'  
**Subject:** NDA 022562: Carbaglu - Communication of Post Marketing Requirements

Dear Dr. Leonardi,

Reference is made to NDA 022562 for Carbaglu (carglumic acid) Tablets. Please be advised that Orphan Europe will be required to conduct the following Post Marketing Requirements (PMRs):

1. a chronic (9-month) oral toxicology study in a non-rodent species;
2. a 2-year carcinogenicity study in a single rodent species;
3. in vitro studies to assess the potential for drug-drug interactions by identifying the enzymes that mediate the metabolism of carglumic acid;
4. in vitro studies to assess the potential for carglumic acid to inhibit or induce CYP isoenzymes;
5. a registry of patients with NAGS deficiency being treated with carglumic acid to obtain long-term clinical safety information. Data to be collected will include patient demographics, details of treatment with carglumic acid, other therapies for hyperammonemia and dietary protein management, clinical status, neurocognitive and psychomotor outcomes, growth and development stages, and adverse events. Information from this registry should be submitted annually (in annual reports) with a final report submission at 15 years post-approval.
6. a study of the effects of carglumic acid on pregnancy and fetal outcomes. This study can be performed as a sub-study within the registry described above. Information on pregnancy and fetal outcomes should be submitted annually (in annual reports) and included in the final report submission on the registry at 15 years post-approval.

For each PMR, please submit, to your NDA, a timetable identifying the following milestones dates:

- Final Protocol Submission Date
- Study Completion Date
- Final Report Submission Date

Please provide a response by February 16, 2010.

Best Regards,

*Roland Girardet, MHS, MS, MBA*  
*Regulatory Project Manager*  
*Division of Gastroenterology Products*

*Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: [roland.girardet@fda.hhs.gov](mailto:roland.girardet@fda.hhs.gov)*

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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ROLAND GIRARDET  
02/09/2010

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Monday, February 01, 2010 2:35 PM  
**To:** 'ron@rrregs.com'  
**Cc:** Ann wk email  
**Subject:** NDA 22562: Request for Container Labeling

Dear Dr. Leonardi,

We are in the process of reviewing the carton and container labeling for NDA 022562 and request that you submit samples of your 5 and 60 count containers with the proposed container labeling which you plan to use in the U.S. marketed product, affixed to each container. Please submit two copies of each bottle plus affixed labeling to the NDA via the document room and express mail one copy of each bottle plus affixed labeling to my physical address as indicated below.

Document Room Address:

Donna Griebel, M.D.,  
Director  
Division of Gastroenterology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Physical Address:

Roland Girardet  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER, White Oak Campus, Bldg 22, Rm. 5143  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

In order to continue reviewing your application, a prompt response is requested. If you have any questions, please feel free to contact me at 301-796-3827.

Best Regards,

*Roland Girardet, MHS, MS, MBA*  
*Regulatory Project Manager*  
*Division of Gastroenterology Products*  
*Office of Drug Evaluation III*  
*Center for Drug Evaluation and Research*  
*U.S. Food and Drug Administration*  
*10903 New Hampshire Ave.*  
*Silver Spring, MD 20993-0002*  
*Phone: (301) 796-3827*  
*Email: roland.girardet@fda.hhs.gov*

2/1/2010

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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ROLAND GIRARDET  
02/01/2010

# REQUEST FOR CONSULTATION

TO (Office/Division): **Pediatric and Maternal Health Staff (PMHS)**

FROM (Name, Office/Division, and Phone Number of Requestor): **Roland Girardet, Regulatory Project Manager, ODE III/Division of Gastroenterology Products (DGP), 301-796-3827**

DATE  
01/08/2010

IND NO.

NDA NO.  
22-562

TYPE OF DOCUMENT  
Package Insert

DATE OF DOCUMENT  
06/17/2009

NAME OF DRUG  
**Carbaglu (carglumic acid) Tablets**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
02/08/2010

NAME OF FIRM: **Orphan Europe, S.A.R.L.**

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The Division of Gastroenterology Products (DGP) requests assistance in reviewing the Pregnancy and Nursing Mothers sections of the proposed package insert for NDA 22-562: Carbaglu (carglumic acid) Tablets, 200 mg. The sponsor's complete proposed draft package insert and the Pharmacology/Toxicology reviewer's recommended version of the Pregnancy and Nursing Mothers sections is attached. In addition, we will provide a draft nonclinical review under separate cover. Please let me know if any additional information will be necessary to aid in your review. We request that you provide comments and edits to the proposed version from the Pharm/Tox reviewer since the sponsor's version is not well written.

-Roland Girardet, RPM, 301-796-3827

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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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ROLAND GIRARDET  
01/08/2010



NDA 22-562

**INFORMATION REQUEST**

Orphan Europe, SARL  
c/o R & R Registrations  
Attention: Ronald G. Loenardi, Ph.D.  
President  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbaglu (carglumic acid) Tablets, 200 mg.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the concentrations and stoichiometry of the reaction components for the drug substance synthesis. Also, provide a discussion of process controls for the synthesis.
2. Please revise the acceptance limit for (b) (4) to NMT (b) (4) for both drug substance and product. Revise the drug substance specifications to include the chiral HPLC assay. If a higher acceptance limit is necessary, provide a toxicology assessment and adequate justification. Is the (b) (4) biologically active as an allosteric activator of carbamoyl phosphate synthetase? Regarding the chiral purity assay, provide the structure of the derivative formed by reaction of (b) (4) with carbaglu along with supporting characterization data.
3. Provide a postapproval stability protocol and stability study commitment for the drug substance.
4. Regarding the drug product specifications, tighten the specification limit for disintegration time to NMT 1 min and the dissolution limit to  $Q = (b) (4)$  at 15 min. Regarding impurity testing, explain the instruction to disregard the impurity peaks designated (b) (4) in the test instructions for the HPLC method.
5. Regarding drug product stability, provide a commitment to add one drug lot per year to the stability program post approval along with a complete description of the stability

protocol to be used. Also, repeat accelerated testing at 40°C/75%RH because the reported results are too limited (only 2 lots) and not consistent.

6. Regarding labeling, include the molecular formula in the Description section and the tablet strength in the How supplied section. Include instructions for dispersal of the tablets in water.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Roland Girardet, Regulatory Project Manager the Office of New Drugs (Roland.Girardet@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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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MOO JHONG RHEE  
01/07/2010  
Chief, Branch III

**Girardet, Roland**

---

**From:** Girardet, Roland  
**Sent:** Tuesday, November 10, 2009 9:03 AM  
**To:** 'ron@rrregs.com'  
**Cc:** ann@rrregs.com  
**Subject:** NDA 022562: Information Request 11\_10\_09  
**Attachments:** 11\_10\_09 Informatin Request.doc

Dear Dr. Leonardi,

Attached, please find a clinical information request for the Carbaglu NDA. This information request includes some general as well as patient-specific questions.

If you have any questions, please feel free to contact me at your convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

## ORPHAN EUROPE QUESTIONS

We have identified the following questions based on our review of your submission (NDA 22-562).

### GENERAL

1. Please clarify how you determined the reference range(s) used for glutamine. Also, please clarify if patient age or time of sampling affected your choice of reference range.
2. Some patients have elevated glutamine levels at their “control visit”. What does a control visit involve? Is medication (e.g. carglumic acid) withheld for a period of time? Please clarify so we can understand why the levels rise during the control visit and then go back to normal so quickly. Note this applies to other measurements as well, such as ammonia levels.
3. Please clarify the discrepancies in the ranges for normal in ammonia values listed in the electronic data sets and narratives (see also below).
4. Please clarify how you determined reference range(s) for plasma citrulline levels, and include information on change in normal reference ranges based on age.

### PATIENT 1 (b) (6)

- There was an elevated glutamine level of 1043  $\mu\text{mol/L}$  at a “control visit” on May 10, 2001. Please clarify what you mean by “control visit”. Was the carglumic acid withheld for some period of time prior to the blood sampling? Was there a question of non-compliance that might explain the elevated level?

### PATIENT 2 (b) (6)

- There was an elevated glutamine level of 1147  $\mu\text{mol/L}$  at a “control visit” in November of 1993. The next day the level was 557  $\mu\text{mol/L}$ . Was the carglumic acid withheld for some period of time prior to the blood sampling? Was there a question of non-compliance that might explain the elevated level?

### PATIENT 3 (b) (6)

- The patient had normal ammonia levels as of the last “control” in 2007. Please clarify what “control” means in this context. What specific studies are performed at a “control” visit, if any?

### PATIENT 5 (b) (6)

- Arginine was given until the last recorded “control” in 2007. Please clarify what “control” means in this context. What specific studies are performed at a “control” visit, if any?

- How was this patient's dietary protein restricted? The only information provided states that the patient was exclusively breast fed in the neonatal period. Please clarify if any special formulas or other protein-restricted diets were used.

PATIENT 6 (b) (6)

- Please clarify what you mean by saying the patients ammonia levels normalized within 24 hours of therapy with carglumic acid that began December 15, 1996. In the same sentence you refer to a normal range as  $<90 \mu\text{mol/L}$  and give the date April 21, 1997. In the electronic datasets you provide a reference range for plasma ammonia of 50-150  $\mu\text{mol/L}$ . Please provide the scientific basis for this unusual reference range. Please also explain why this same reference range is not used in the other patients.

PATIENT 7 (b) (6)

- At the time of the patient's fourth decompensation (June, 1997) she was treated with sodium benzoate, arginine, IV, as well as protein-free, high caloric enteral feedings. Arginine and citrulline appear to have been started at the same time. Please clarify what specific treatments were given (including dose, time of initiation, etc.) during the patient's fourth episode of decompensation when the ammonia level was 221  $\mu\text{mol/L}$ .

PATIENT 13 (b) (6)

- You state that this patient's citrulline levels are "very low" (e.g. 3 mmol/L) before treatment is initiated with carglumic acid at day of life (DOL) 4. However, this appears to be a normal citrulline levels during the new born period ( $< 1$  month of age). Please clarify and identify the reference ranges for normal (by age) you include here.
- Please clarify the specific type of hypercaloric diet that was initiated in this patient (e.g., IV glucose).
- Please explain why in the case of Patient 13 a normal level was documented as  $< 90 \mu\text{mol/L}$ . Please also explain why this same reference range is not used in the other patients.
- What low dose of carglumic acid that did the patient receive that led to a hyperammonemic episode early in treatment.
- Why did the patient receive one week of concomitant therapy with domperidone?

PATIENT 15 (b) (6)

- Please explain the apparent discrepancy between the patient narrative and electronic datasets, and subject profile in the initial date and dose of carbaglu for this patient.
- Please explain the apparent discrepancy between statements in the narrative and electronic data sets regarding this patient's ammonia levels. The narrative appears to indicate that the patients maintained ammonia levels within normal limits, however, ammonia levels in the data sets show elevations at several timepoints.
- When was the dose of carglumic acid reduced to 12 mg/kg?

- Please explain the apparent discrepancy between statements in the narrative and the subject profile. In March 2003, the patient had reinitiation of sodium phenylbutyrate at a dose of 1200 mg/d then reduced to 300 mg/d according to the narrative. However, the subject profile states that sodium phenylbutyrate was given only from August 7, 1999 through June 19, 2001.

PATIENT 16 (b) (6)

- What imaging study was used to confirm this patient's focal cerebral edema? Please provide reports of all brain imaging studies for this patient.
- Please characterize the nature of the EEG focal abnormality. Were there PLEDS (periodic lateralized epileptiform discharges) one see with herpes encephalitis or was some other form of epileptiform discharge present?

PATIENT 26 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- Please provide details regarding the diagnosis of NAGS deficiency in this patient. The narrative states that the physicians suspected NAGS deficiency based on the combination of hepatomegaly and hyperammonemia, along with a positive family history for NAGS deficiency.

PATIENT 28 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- Please provide details regarding this patient's diagnosis of McLeod Syndrome (this normally is diagnosed much later in life (50 yrs)).
- Please provide details regarding the interpretation of the patient's liver biopsy results. It appears that the liver biopsy does not confirm NAGS deficiency.
- Please provide DNA test for NAGS deficiency for this patient. If this test was not performed, please explain why this test was not performed.
- Please explain the apparent discrepancy between statements in the narrative and the subject profile. The patient was started on sodium benzoate according to the narrative in 1993. However, the subject profile states that sodium benzoate was given on May 29 and May 30, 2002 at a dose of 1500 mg and 250 mg, respectively.
- Please clarify the starting date and dose of carnitine.

PATIENT 29 (b) (6)

- Please provide details regarding the patient's protein-restricted diet (e.g., clarify by what amount, how, and when the protein was restricted).
- Please explain the apparent discrepancy between statements in the narrative and the subject profile. The narrative states that a normal head MRI and CT scan were obtained on October 30, 1993; however, the subject profile does not contain any information regarding these studies.
- Please provide DNA test for NAGS deficiency for this patient. If this test was not performed, please explain why this test was not performed.

- Explain why the liver biopsy was not repeated if the results were equivocal.

PATIENT 30 (b) (6)

- Please provide any birth or family history available on this patient.
- Clarify the dosing information you have regarding the patient's treatment with the chemical grade carbamyl glutamate he received reportedly since 1987 before switching to pharmaceutical grade carginic acid.
- Please explain the apparent discrepancy between statements in the narrative and the subject profile regarding use of carbaglu during an episode of decompensation in 1995. The subject profile states that the patient received carbaglu, but the patient narrative does not mention treatment with carbaglu.
- Please clarify dosing and dose frequency of sodium benzoate and arginine in this patient.

PATIENT 33 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- Please clarify the initial dosing of phenobarbitone, L-carnitine, and sodium benzoate given May 8, 1996.
- Please explain the apparent discrepancy between statements in the narrative and the subject profile. The initial dose of carginic acid from the subject profile appears to be 250 mg, t.i.d, but the narrative does not state a specific dose.
- Please clarify the early phases of dosing of carginic acid, and if possible, when the patient was switched from chemical to pharmaceutical grade carginic acid.

PATIENT 35 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- Please clarify the dose, dose frequency, and duration of carbamazepine for this patient.
- Please clarify what antibiotic treatment this patient received (what drugs, how much, how frequently and for how long) in December 2003.
- Please explain the apparent discrepancy between statements in the narrative and the subject profile. The narrative states that IV arginine given on December 4, 2003, however, there is no mention of the IV arginine given in the subject profile.
- Please provide results of all brain MRIs performed on this patient. The narrative describes a normal MRI but does not specify whether this was a brain MRI.

PATIENT 36 (b) (6)

- Please provide information regarding the patient's birth or family history, if available. We note that the patient's birth weight of 2170 g, is small for a full-term newborn.
- The narrative notes that the patient underwent a protein restricted diet initially set at 12 g/day, however, the subject profile states that the dose was 15 g/d on November 1, 1999. Please explain this apparent discrepancy.

- Please provide information of use of concomitant therapy, if any. Specifically, did this patient ever receive carbaglu as monotherapy, and if so, please provide details.
- The starting dose of citrulline appears to have been 2 g/day (March 2004). Please explain the use of citrulline in this patient and whether this dosing information is correct. Clarify why this intervention was done and if the dosing information is correct. Also, please clarify whether citrulline was stopped in June 2007.
- Please provide details regarding the patient's recurrent increases in blood ammonia and glutamine.

PATIENT 39 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- In March 2005, the patient presented with psychiatric symptoms. What did these symptoms entail (e.g. agitation, disorientation, etc.) on initial presentation besides hyperactivity if anything?

PATIENT 43 (b) (6)

- Please provide information of use of concomitant therapy, if any.

PATIENT 60 (b) (6)

- Please provide information regarding the patient's birth history or family history, if any.

PATIENT 61 (b) (6)

- Please provide information regarding the patient's birth or family history, if available. We note that the patient's birth weight of 1980 g, is very small for a full-term newborn.
- Please clarify what imaging studies of the brain were done to confirm cerebral atrophy. Was there any follow-up imaging (e.g., CT or MRI) on the brain? Please provide all brain imaging results and readings for this patient to confirm that the patient had cerebral atrophy.
- Please clarify whether the patient had an EEG performed to characterize the seizure disorder. If so, please provide the date and results of the test.
- Please clarify when concomitant therapy was initiated in this patient to help control ammonia, what doses were given and when various medications were stopped. It appears that arginine and carnitine were only given for two days. The information provided in the narrative is unclear.
- Why did the patient undergo hemodialysis?

PATIENT 74 (b) (6)

- Please provide information regarding the patient's birth or family history, if available.
- Please clarify the dates of the initiation of the carglumic acid therapy. The narrative refers to both May 21 and May 29 2007. The subject profile says May 31.

- There are only three data points in the electronic dataset for the dosing of carglumic acid for this patient. How many times was the patient's dose of carblumic acid changed? Please confirm all dosing changes for carglumic acid for this patient.
- The graph provided to illustrate ammonia values for the patient both before and following exposure to carglumic acid appears to be missing some data points. Please explain the apparent discrepancy between the graph and the data contained in the electronic datasets.

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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ROLAND GIRARDET  
11/10/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Wednesday, November 04, 2009 10:54 AM  
**To:** ron@rrregs.com  
**Cc:** 'ann@rrregs.com'  
**Subject:** NDA 022562: Request for Samples

Dear Dr. Leonardi,

The Division would like to request samples of Carbaglu. We understand that Carbaglu is available in 5 count and 60 count bottles. Please send either 3 of the 5 count bottles or one of the 60 count bottles.

Also, please send one sample of the proposed to-be-marketed bottle and cap.

If you have any questions, please feel free to contact me at your earliest convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

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  
11/04/2009



NDA 022562

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Orphan Europe, SARL  
c/o R & R Registrations  
9915 Caminito Chirimolla  
San Diego, California 92131

ATTENTION: Ronald G. Leonardi, Ph.D.  
President, R & R Registrations

Dear Dr. Leonardi:

Please refer to your New Drug Application (NDA) dated June 17, 2009, received June 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carglumic Acid Tablets, 200 mg.

We also refer to your July 30, 2009, correspondence, received July 31, 2009, requesting review of your proposed proprietary name, Carbaglu. We have completed our review of the proposed proprietary name, Carbaglu and have concluded that it is acceptable.

The proposed proprietary name, Carbaglu, will be re-reviewed if this NDA is not approved on or before the December 18, 2009 goal date. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 30, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Roland Girardet at 301-796-3827.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST  
10/28/2009



NDA 22-562

**PDUFA GOAL DATE EXTENSION**

Orphan Europe SARL  
c/o R & R Registrations, U.S. Agent  
Attention: Ron Leonardi, Ph.D.  
President  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

Please refer to your June 17, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbaglu (carglumic acid) Tablets, 200 mg.

On October 15, 2009, we received your October 14, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 18, 2010.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely yours,

*{See appended electronic signature page}*

Matthew Scherer, M.B.A.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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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MATTHEW C SCHERER  
10/22/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Tuesday, September 22, 2009 4:40 PM  
**To:** ron@rrregs.com  
**Cc:** 'ann@rrregs.com'  
**Subject:** Dr. Tuchman Information Request - Part 2  
**Attachments:** Medel Tuchman questions part 2.doc

Dear Dr. Leonardi,

Attached please find a second information request regarding data in Dr. Tuchman's IND - 68,185. If you have any questions or require further information in order to provide a response, please feel free to contact me at your convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

## QUESTIONS MENDEL TUCHMAN PART 2

DATE: 21-September-2009

IND: 68,185

We have the following additional questions regarding Dr. Mendel Tuchman's data as presented in the February, 2009, interim Clinical Study Report.

### GENERAL

1. Please provide a final Clinical Study Report on IND 68,185. If there is no final clinical study report, please explain, and provide any additional summary reports that are available.
2. Please provide reference ranges for all laboratory studies performed (e.g. ammonia etc.).
3. Your study lists the following **safety endpoints**:
  - a. CBC
  - b. BUN, creatinine
  - c. Plasma amino acids

The safety endpoint data (CBC, BUN and creatinine) are missing from the report. Please provide information on the safety endpoints. Additionally, the interim study report only includes information on some amino acids like glutamine, alanine, and glycine, but these were not measured in all patients and there is not panel of overall amino acid results.

4. Please provide the statistical analysis plan for the study if you have one more recent than that submitted in March of 2006. Please explain how the specific p-value was derived from the two-tailed test for each of the seven patients. In a number of cases the p values do not seem to correspond to the actual changes in the urea, glutamine, ammonia, glycine, and alanine levels. For example, Subject 1 has an ammonia level ( $\mu\text{mol/L}$ ) that goes from  $47.0 \pm 25.2$  to  $10.0 \pm 1.7$  with a p value of 0.064, whereas Subject 5 goes from an ammonia level of  $58.0 \pm 5.5$  to  $48.3 \pm 4.8$  with a p value of  $1.2 \times 10^{-3}$ .
5. In the four patients (Subjects 4-7) with propionic acidemia, why did you choose alanine levels as a primary endpoint? What is the relationship between alanine and propionic acidemia? Were you evaluating any specific relationship between alanine and glycine levels in the study?

### SUBJECT 3

6. This a 58 year old patient who experienced from the age of 40 years symptoms such as nausea, headaches, and confusion, but the interim study report on IND 68,185 in the NDA 22-562 submission states her ammonia levels were said to be normal from the age of 40 up until her inclusion in the study (p. 13 February 27, 2009 interim study report.). Information submitted in March of 2006 under IND 68,185 indicates she was hospitalized for attacks with associated hyperammonemia several times over the 17 year period from age 40 to age 58. We assume the study report meant to say 'continuously abnormal' rather than

“continuously normal” but would appreciate clarification. Her pre-Carbaglu ammonia at baseline was 105 ( $\mu\text{mol/L}$ ).

7. Can you explain the p value on a two tailed test for urea measured before and after three day exposure to Carbaglu? The p-value appears too low for the changes in the urea values

#### SUBJECT 7

8. This patient with propionic academia has an elevation in his glycine level following exposure to Carbaglu, the opposite of what one would expect. Please provide an explanation for this finding.

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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ROLAND GIRARDET  
09/22/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Thursday, September 17, 2009 2:47 PM  
**To:** ron@rrregs.com  
**Cc:** 'ann@rrregs.com'  
**Subject:** Carbaglu Information Request 9/17/09  
**Attachments:** Mendel Tuchman questions.doc

Dear Dr. Leonardi,

Attached, please find an information request relating to the clinical studies performed by Dr. Tuchman under IND 68,185.

If you have any questions or require further clarification, please feel free to contact me at your earliest convenience.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

We have reviewed the report from IND 68,185 that contains Dr. Mendel Tuchman's data on the three day study using Carbaglu to examine its effects on hyperammonemia and ureagenesis.

We note the following areas where limited data are provided in the interim clinical study report entitled "Experience with carbamylglutamic acid (Carbaglu) in the US; Ureagenesis restoration in hyperammonemic patients" from February 27, 2009:

- Adverse event data
- Clinical information regarding presentation and treatment history
- Footnotes that do not contain corresponding references (Subjects 3 and 4)
- No references to the use of any validated scales on developmental outcome

We additionally note that a complete protocol for this study was not included in the interim clinical study report. Please provide us with a complete protocol for this study.

We have additional questions regarding the study below. Please provide as much information in response to these questions as possible.

#### GENERAL QUESTIONS

- Why did Subjects 1 and 2 received tracer  $^{15}\text{NH}_4\text{Cl}$ , while patients 3-7 received the  $[1-^{13}\text{C}]$  sodium acetate tracer.
- What form of Carbaglu was used in the study (e.g., powder or other formulation, chemical or pharmaceutical grade)? Also, was the drug product provided by Orphan Europe?
- What specific exclusion criteria, if any, were provided in the protocol? The clinical study report states that none of the patients were acutely ill during the study, but specific study exclusion parameters could not be located in the submission.

#### QUESTIONS REGARDING SUBJECT 1

- This patient was treated along with her sister under emergency INDs 76,291 and 76,292 starting in March of 2007. Following your study they began receiving long-term therapy with N-carbamylglutamate in powder form from (b) (4) (b) (4).
  - What is the birthdate for Subject 1?
  - Which IND belongs to which patient?
  - When did Subject 1 enroll in the study under IND 68,185?
  - Was the dose of 2.2 g/m<sup>2</sup>/day divided bid under INDs 76,291 and 76,292?
  - Do you believe her neurologic spastic diplegia with partial paralysis of the lower extremities in Patient 1 as reported under IND 76,292 was due to exposure to citrulline and the secondary neurotoxic effects of its metabolite, arginine?
  - No adverse events were reported. Can we say that the Carbaglu was well tolerated?

#### QUESTIONS REGARDING SUBJECT 2

- This patient is reported to be a healthy 51 year-old female. Do you have any information on her clinical presentation that led to the suspicion of her clinical diagnosis other than the fact that she was the mother of Subject 1?
- Do you have any information about treatment history for hyperammonemia prior to her participation in the 3 day Carbaglu study?

#### QUESTIONS REGARDING SUBJECT 3

- Do you have information about her dietary modifications during her initial presentation?
- Where is the literature reference on this patient located in the submission? The footnote refers to a reference that was not included.

#### QUESTIONS REGARDING SUBJECT 4

- Where is the literature reference on this patient located in the submission? The footnote refers to a reference that was not included.
- What special formula did this patient receive once the diagnosis of propionic acidemia was established?
- Is there information about the dose of carnitine and biotin he was receiving?
- This subject experienced adverse events that involved rhinorrhea, coughing, vomiting, and eventually a diagnosis of strep throat. When was the strep throat diagnosed?

#### QUESTIONS REGARDING SUBJECT 5

- What specific laboratory tests confirmed the diagnosis (i.e., urine organic acid analysis)?
- What seizure medicine(s) were used from the age of two weeks to one year of life on this patient and what type(s) of seizures did this patient have?
- What were the various medications and dietary modifications that comprised the patient's treatment before entering the study?

#### QUESTIONS REGARDING SUBJECT 6

- What medications other than L-carnitine, biotin, and dietary modifications were used to treat the patient's dilated cardiomyopathy in the newborn period?
- Can you provide more specific details regarding dosing of L-carnitine and dietary modifications in this patient?

#### QUESTIONS REGARDING SUBJECT 7

- Can you clarify the nature of the special formula and the amount of L-carnitine the patient was receiving prior to entering the study?
- Please explain the presumed or confirmed cause for this patient's recurrent pancreatitis.

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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ROLAND GIRARDET  
09/17/2009



NDA 22-562

**FILING COMMUNICATION**

Orphan Europe SARL  
c/o R & R Registrations, U.S. Agent  
Attention: Ron Leonardi, Ph.D.  
President  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

Please refer to your new drug application (NDA) dated June 17, 2009, received June 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Carbaglu (Carglumic Acid) Tablets, 200 mg.

We also refer to your submissions dated July 29, 2009, August 3, 2009, August 6, 2009 and August 12, 2009.

During our filing review of your application, we identified the following potential review issues:

Due to the nature of this submission, there will likely be clinical issues identified throughout the review cycle that will require additional clarification, verification, or information from you. We anticipate that these issues will include requests for additional information regarding:

1. Adverse events (AEs), including treatment interventions for AEs and their outcomes.
2. Characterization of patients' neurological psychomotor status.
3. Dosing and dosing modifications for Carbaglu and concomitant medications.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

### Clinical Pharmacology

1. Provide a SAS file for individual PK parameters for healthy subjects. If this information is already submitted, please provide its location in the submission. The format and definition of each variable should be separately provided and clearly explained. For example, in your previous submission of a SAS file of PK in patients dated April 30, 2008, the format of date of 1<sup>st</sup> dose-day 1 (code: ddday11) was defined as DDMMYY. However, the actual data in the SAS file was 16056 for a subject PATNO16. As such, this information was not interpretable.
2. Provide information on the dose administered to patients in the tables of plasma concentrations in patients, and plasma ammonia and glutamate levels at baseline and during/after treatment (pages 19 and 20 in section 2.7.)
3. Provide a new copy of the information listed below, as the current copies are illegible:
  - a. Module 2: Section 2.7, Table titled “Results of the assays” on page 22 of 53, and Section 2.6 Figure 11.
  - b. Module 5: Report 8, Table 4 in volume 1.5.
4. We note that genotyping was conducted for patients during treatment. Please provide relevant information including, but not limited to, genotyping methods, genotyping results, and the effect of genotype on the responses to treatment, such as changes in plasma ammonia and glutamate levels. If such information is already submitted, please provide the location of this information in the submission.
5. Clarify how the powder formulation was administered to patients in relation to meals, e.g., before or after meals?

### Nonclinical

6. Patients taking Carbaglu will be exposed to high levels of excipients due to the need for daily ingestion of a large number of tablets to achieve the recommended dose levels (e.g., up to 75 tablets/day in a 60-kg patient). Please provide safety information (animal and/or human) on the following two excipients: croscarmellose sodium and sodium stearyl fumarate. Because of the chronic nature of the proposed indication, we are particularly interested in information that supports the safety of these excipients in chronic use. The information can be in the form of publications.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting, Chief Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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CRISTI L STARK  
08/31/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Thursday, August 27, 2009 1:19 PM  
**To:** ron@rrregs.com  
**Cc:** 'ann@rrregs.com'  
**Subject:** Question regarding clinical study under IND 61,265

Hi Ron,

The medical officer reviewing the Carbaglu application asked me to check with you regarding the status/history of a study which was proposed under the original Orphan Europe IND: 61,265. According to information in the original IND submission dated July 8, 2003, Orphan Europe was proposing a year-long clinical study titled, "Carglumic acid (N-carbamoyl-L-glutamic acid, Carbaglu) in therapy of hyperammonemia due to N-acetylglutamate synthase deficiency: A treatment protocol" to be conducted nation-wide in the U.S. and coordinated by Dr. Tuchman out of Children's National Medical Center.

Do you know if this study ever took place and if so, were the results submitted as part of the current NDA application? Any information you could provide regarding this study would be very helpful.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

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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ROLAND GIRARDET  
09/17/2009



NDA 22-562

**PRIORITY REVIEW DESIGNATION**

Orphan Europe SARL  
c/o R & R Registrations, U.S. Agent  
Attention: Ron Leonardi, Ph.D.  
President  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

Please refer to your new drug application (NDA) dated June 17, 2009, received June 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Carbaglu (carglumic acid) Tablets, 200 mg.

We also refer to your submissions dated July 29, 2009, August 3, 2009, August 6, 2009 and August 12, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 18, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 18, 2009.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before August 31, 2009.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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CRISTI L STARK  
08/17/2009

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 22-562 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Carbaglu (pending review) Established/Proper Name: Carglumic Acid (INN approved name), (pending USAN approval) Dosage Form: Tablet Strengths: 200 mg		
Applicant: Orphan Europe Agent for Applicant (if applicable): R & R Registrations		
Date of Application: 6/17/09 Date of Receipt: 6/18/09 Date clock started after UN:		
PDUFA Goal Date: 12/18/09	Action Goal Date (if different):	
Filing Date: 8/17/09 Date of Filing Meeting: 7/23/09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): Treatment of Hyperammonemia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b>Refer to Appendix A for further information.</b>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input checked="" type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 61,265	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a>  <b>If yes, explain:</b>  <b>If yes, has OC/DMPQ been notified of the submission?</b>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  <b>Comments:</b>	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If yes, please list below:</b></p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p><b>Format and Content</b></p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>		<p>Datasets + COL</p>	
<p><b>If electronic submission:</b>  paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> A separate establishment description form was submitted in module 1 (1.4.3)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b> A consult was sent to the Controlled Substances Staff because the drug crosses the blood-brain barrier.</p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></b></p> <p><b>Note:</b> Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<b><i>applies to paper submissions only</i></b>)</p> <p><b>Comment:</b> <i>This is a foreign applicant so the field copy was sent to headquarters.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><b>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</b></p> <p><b>Note:</b> Financial disclosure is required for bioequivalence studies that are the basis for approval.</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b>  <b>Note:</b> NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no,</b> is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <b>If no,</b> request in 74-day letter.</li> <li>• <b>If yes,</b> does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	

<b>Comments:</b>	
<b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? <b>Comments:</b> Upon request from the Division, the sponsor submitted a request for trade name review on 8/3/09.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s):4/28/04 and 9/26/09 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 7/23/09

**NDA/BLA #:** 22-562

**PROPRIETARY/ESTABLISHED NAMES:** Carbaglu (Carglumic Acid)

**APPLICANT:** Orphan Europe c/o Ron Leonardi, Ph.D., US Agent

**BACKGROUND:** Carbaglu (carglumic acid) Tablets, 200 mg is a new molecular entity intended for the treatment of hyperammonemia related to N-Acetylglutamate synthase (NAGS) deficiency, a rare autosomal recessive genetic disorder. This drug was approved in Europe by the EMEA in 2003. The applicant is Orphan Europe SARL, which is located in France and is represented by U.S. Agent, Ron Leonardi, Ph.D., from R&R Registrations. Give the rare nature of the disease, the application relies on a retrospective case-report series rather than the standard double-blind, placebo-controlled, prospective studies which typically support an application.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Roland Girardet, M.H.S., M.S., M.B.A.	Y
	CPMS/TL:	Cristi Stark, M.S.	Y
Cross-Discipline Team Leader (CDTL)	Lynne Yao, M.D.		Y
Clinical	Reviewer:	Virginia Elgin, M.D.	Y
	TL:	Lynne Yao, M.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Insook Kim, Ph.D.	Y
	TL:	Sue Chih Lee, Ph.D.	Y
Biostatistics	Reviewer:		
	TL:	Mike Welch, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yuk-Chow Ng, Ph.D.	Y
	TL:	David Joseph, Ph.D.	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Martin Haber	Y
	TL:	Marie Kowblansky	N
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>If yes, list issues:</b>	

Per reviewers, are all parts in English or English translation?  <b>If no</b> , explain: See clinical comments below.	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
---	--

<b>Electronic Submission comments</b>  <b>List comments:</b> The application was all in paper format with the exception of the labeling which was submitted in SPL format.	<input checked="" type="checkbox"/> Not Applicable
--	--

<p><b>CLINICAL</b></p> <p><b>Comments:</b> During the Filing Meeting the Clinical Reviewer spent considerable time explaining the challenges with the application. Specifically, she noted that while most of the application had been translated, there still remained portions of the application which were in foreign languages. She also brought to the team's attention, the fact that the clinical information necessary for review was poorly organized in that information on each patient was dispersed throughout the application. As a result, it would be very challenging to ascertain clinical information on each patient, which would be necessary in order to complete a clinical review. After considerable discussion with the team, the decision was made to contact the sponsor to see if it was possible for them to submit information on patient-by-patient basis and if so, to find out how long it would take them to do so. The decision on fileability would be partially dependent on the sponsor's ability to provide information in the requested format. Therefore the decision on whether or not to file the application was deferred until further discussion with the sponsor had taken place.</p> <p>On July 27, 2009, a teleconference was held with the sponsor in which the stated they could supply the division with the clinical information on a per-patient basis. They submitted this information electronically on August 3, 2008. Based on a review of the information, the clinical reviewer determined that the information submitted appeared to be reviewable.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
--	---

<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> The drug is an NME. The study forming the</p>	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO
--	--

<p>basis for approval is a retrospective case-report series of 23 patients who received Carbaglu at multiple sites in Europe over 15 years. The drug was not administered under IND.</p>	<p><input type="checkbox"/> To be determined Reason: See Comments</p>
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> The Clinical Pharmacology Reviewer noted that a few documents she needed to review contained some information in foreign languages. Also she noted that clinical pharmacology site inspections would be necessary.</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>BIostatISTICS</b></p> <p><b>Comments:</b> A biostatistical review is not possible because this was a case series study where, at most, only descriptive statistics were captured. Therefore, no formal statistical analysis can be performed.</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> The Nonclinical Reviewer noted the need to consult the Controlled Substances Staff. He also, noted that there was an outstanding request to perform a 9 month Chronic Toxicity Study; however, that this study could be addressed as a post-marketing requirement rather than a filing issue.</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE</p>

<p><b>Comments:</b> The CMC Reviewer stated that the application was fileable from a CMC perspective.</p>	<input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li>   <li><b>If no</b>, was a complete EA submitted?</li>   <li><b>If EA submitted</b>, consulted to EA officer (OPS)?</li>   <li><b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li>   <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li>   <li><b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?</li>   <li><b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Office Director</p> <p><b>GRMP Timeline Milestones:</b>  Application Receipt: June 18, 2009  Filing Meeting: July 23, 2009  Filing Letter: August 18, 2009  74 Day letter: August 31, 2009  Mid-cycle Meeting: October 23, 2009  Wrap-up Meeting/Communicate PMRs/PMCs: Mid-November  Action Date: December 18, 2009</p>	

<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/  
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ROLAND GIRARDET  
08/14/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Thursday, August 13, 2009 1:51 PM  
**To:** ron@rrregs.com  
**Cc:** 'ann@rrregs.com'; Ton, Phuong Nina  
**Subject:** Carton and Container label mockups for Carbaglu

Dear Ron,

Thank you for submitting the Request for Proprietary Name Review for Carbaglu. I received a request from the team which reviews these types of submissions to get different carton and container mock-ups. Typically applicants submit mockups of the carton and container labeling that closely replicate the labeling that the sponsor proposes to introduce into the market. These full mockups allow the reviewers to view all visual aspects of the carton and container labeling (Background Color, Font Color, Font Style, Text Size, Text Spatial Orientation, etc....) with respect to the physical constraints of the carton and container labels (sizes, shapes, folding specs, etc...).

The carton and container label information submitted as part of Carbaglu NDA only contains the proposed text. We request that you submit full color mockups in English of the carton and container labeling to allow the timely review of this material.

If you have any questions, or require clarification in order to respond, please let me know.

Best Regards,

*Roland Girardet, MHS, MS, MBA  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: roland.girardet@fda.hhs.gov*

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/s/  
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ROLAND GIRARDET  
08/13/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising, and Communications (DDMAC)**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Roland Girardet, Regulatory Project Manager,  
OND/ODE III/Division of Gastroenterology Products  
(DGP), Phone: 301-796-3827**

DATE  
8/12/09

IND NO.

NDA NO.  
22-562

TYPE OF DOCUMENT  
Package Insert for New  
Drug Application

DATE OF DOCUMENT  
6/17/09

NAME OF DRUG  
**Carbaglu (Carglumic Acid)  
Tablet, 200 mg**

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
New Molecular Entity

DESIRED COMPLETION DATE  
2/17/09 (date of 3<sup>rd</sup> labeling  
meeting)

NAME OF FIRM: **Orphan Europe SARL, c/o R & R Registrations, U.S. Agent**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DGP request review of the Package Insert (PI) submitted as part of NDA 22-562. The PI is in PLR format and can be accessed via the following link in the EDR:

\\Fdsww150\nonectd\N22562\N\_000\2009-06-17.

If there are any questions or if more information is required in order to review this material, please contact Roland Girardet, Regulatory Project Manager at 301-796-3827.

SIGNATURE OF REQUESTOR  
**Roland Girardet, Regulatory Project Manager**

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/  
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ROLAND GIRARDET  
08/12/2009

**Girardet, Roland**

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**From:** Girardet, Roland  
**Sent:** Friday, March 12, 2010 2:37 PM  
**To:** R & R Registrations  
**Cc:** 'jennifer Spinella'; 'ann@rrregs.com'  
**Subject:** NDA 022562: Post Marketing Requirements (PMRs) and Post Marketing Commitments (PMCs)

Dear Dr. Leonardi,

Below, please find the Division's final list of PMRs and PMCs for NDA 022562. Please send a response in writing no later than Monday, March 15, 2010 indicating agreement to these items and providing dates were indicated.

**Post Marketing Requirements (PMRs)**

1. A 2-year carcinogenicity study in a single species.

Final Protocol Submission: \_\_\_\_\_  
 Study Completion Date: \_\_\_\_\_  
 Final Report Submission: \_\_\_\_\_

2. A registry of patients, including infants, with NAGS deficiency being treated with carglumic acid to obtain long-term clinical safety information. Data to be collected will include patient demographics, details of treatment with carglumic acid, other therapies for hyperammonemia, dietary protein management, clinical status, neurocognitive and psychomotor status, growth and development status, and adverse events.

Information from this registry should be submitted annually (in annual reports) with a final report submission at 15 years post-approval.

Final Protocol Submission: \_\_\_\_\_  
 Study Completion Date: \_\_\_\_\_  
 Final Report Submission: \_\_\_\_\_

3. A study of the effects of carglumic acid on pregnancy and fetal outcomes. This study can be performed as a sub-study within the registry for all patients with NAGS deficiency. Information on pregnancy and fetal outcomes should be submitted annually (in annual reports) and included in the final report submission on the registry at 15 years post-approval.

Final Protocol Submission: \_\_\_\_\_  
 Study Completion Date: \_\_\_\_\_  
 Final Report Submission: \_\_\_\_\_

**Post Marketing Commitments (PMCs)**

4. We acknowledge your plans to complete and submit the final study report for the on-going study entitled, "*In vitro* metabolic stability of N-carbamyl [14C]-glutamic acid in rat, mini-pig, dog, monkey and human hepatocytes." The

viability of the hepatocytes in terms of various cytochrome P450 enzyme activities should be documented in the report.

Final Report Submission: \_\_\_\_\_

5. An *in vitro* study to assess the potential for carglumic acid to inhibit or induce the Cytochrome P450 enzymes.

Final Protocol Submission:

Study Completion Date: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

If you have any questions, please feel free to call me.

Best Regards,

**Roland Girardet**, MHS, MS, MBA  
*Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
Phone: (301) 796-3827  
Email: [roland.girardet@fda.hhs.gov](mailto:roland.girardet@fda.hhs.gov)*

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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ROLAND GIRARDET  
03/12/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): Office of the Center Director/Controlled Substances Staff (CSS)

FROM (Name, Office/Division, and Phone Number of Requestor): Roland Girardet, Regulatory Project Manager/ODE III/Division of Gastroenterology Products (DGP), Phone: 301-796-3827

DATE 8/5/09	IND NO.	NDA NO. 22-562	TYPE OF DOCUMENT New Drug Application	DATE OF DOCUMENT 6/17/09
NAME OF DRUG Carbaglu (Carglumic Acid) Tablet, 200 mg		PRIORITY CONSIDERATION Priority Review Clock	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE 2/18/09

NAME OF FIRM: Orphan Europe SARL c/o R&R Registrations, U.S. Agent

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |   |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

**COMMENTS / SPECIAL INSTRUCTIONS:** DGP requests consultation from CSS to determine whether or not the Sponsor, Orphan Europe SARL, in their New Drug Application, submitted to the Division on June 17, 2009, needs to address the abuse potential of Carbaglu. And, if so, whether the submitted nonclinical studies adequately address the issue. This is an all paper submission. A copy of Module 4 is available for your review. To coordinate delivery, please contact Roland Girardet, Regulatory Project Manager, 301-796-3827.

Please note, the desired completion date was chosen to match the goal date for the discipline reviews; however, an early determination of whether or not the sponsor needs to address the abuse potential is requested. If possible we would request this determination by 9/6/09.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS     
  EMAIL     
  MAIL     
  HAND

Roland Girardet, Regulatory Project Manager	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/  
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ROLAND GIRARDET  
08/06/2009

**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** 7/30/09

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** (Required for international inspections)  
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader;  
CAPT. E. Dennis Bashaw, Pharm.D. Director, Division of Clinical Pharmacology 3,  
HFD-880

**FROM:** Roland Girardet, Regulatory Project Manager, Division of Gastroenterology Products,  
HFD-180

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 22-562  
Carbaglu (carglumic acid) Tablet, 200 mg  
Orphan Europe, SARL

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
P99148/OE3 12/PK/99-01	Clinical Site : Aster-Cephac 3 &5 Rue Eugen Millon 75015 Paris-France Didier Chassard, M.D. Tel: 01-53-68-08-63	(b) (4) 

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

\_\_\_\_\_ Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **November 18, 2009**. We intend to issue an action letter on this application by **December 18, 2009**.

Should you require any additional information, please contact Insook Kim, Clinical Pharmacology Reviewer, 301-796-2332 or Roland Girardet, Regulatory Project Manager, 301-796-3827.

Concurrence: (Optional)

Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader

Insook Kim, Ph.D., Clinical Pharmacology Reviewer

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

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/s/

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ROLAND GIRARDET  
07/30/2009

SUE CHIH H LEE  
07/31/2009

EDWARD D BASHAW  
07/31/2009

# MEMORANDUM OF TELECON

DATE: 7/24/09

APPLICATION NUMBER: NDA 22-562

**BETWEEN:**

Name: Ron Leonardi, Ph.D., R&R Registrations  
Anne Field, R&R Registrations  
Orphan Europe  
Phone: 800-501-8979  
Representing: Orphan Europe

**AND**

Name: Donna Griebel, M.D., Director  
Anne Pariser, M.D., Acting Deputy Director  
Lynne Yao, M.D., Acting Medical Team Leader  
Virginia Elgin, M.D., Medical Reviewer  
Cristi Stark, M.S., Acting Chief, Project Management Staff  
Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager  
Division of Gastroenterology Products (DGP), HFD-180

SUBJECT: Organization of Clinical Data

**Background:**

Paper NDA 22-562 was received on June 18, 2009. A preliminary review of the submission revealed some deficiencies relating to the organization of the clinical data in Module 5, which needed to be addressed prior to making a filing determination for the NDA. These deficiencies were discussed at the filing meeting on July 23, 2009 and a decision was made to contact the sponsor to ask if they could organize and resubmit all clinical data on a patient by patient basis.

**Discussion:**

FDA stated that a preliminary review of Module 5 of Orphan Europe's drug application, found the clinical data to be difficult to review because the information needed to assess the drug was scattered throughout the submission. FDA asked Orphan Europe to assess the feasibility and time needed to resubmit the clinical information on a patient by patient basis. FDA referred Orphan Europe to the example they had provided in their briefing document submitted for the September 26, 2008, meeting with the Division as being representative of the content and organization which would be needed to perform a review of the material. Orphan Europe stated that they understood what the Agency was requesting and would provide a response early next week with an estimate of how long it would take to comply with FDA's request.

FDA asked Orphan Europe if they had provided data from studies with Carbaglu performed by Dr. Mendel Tuchman as part of their application. Orphan Europe stated that this information had

been submitted as Study #13 in Module 5 (Section 1.15). FDA asked if Orphan Europe had included a letter from Dr. Tuchman, granting them right of reference to use information from his IND as part of their NDA. Orphan Europe stated that they had not provided such a letter as part of their NDA, however, that they would obtain a letter from Dr. Tuchman and submit it as an amendment to the application.

Orphan Europe (Dr. Leonardi) agreed there were problems with legibility and would make attempts where possible to improve the legibility of the submission.

The call ended.

Roland Girardet  
Regulatory Project Manager

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

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/s/  
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ROLAND GIRARDET  
07/28/2009

# DSI CONSULT: Request for Clinical Inspections

**Date:** 7/14/09

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2  
*Khairy Malek, M.D., Medical Officer, GCP1, HFD-46*  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** *Virginia Elgin, M.D., Medical Officer, DGP*  
*Lynne Yao, M.D., Medical Team Leader, DGP*  
*Donna Griebel, M.D., Director, DGP*

**From:** *Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager, DGP*

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 22-562  
Orphan Europe, SARL  
U.S. Agent: Ron Leonardi, Ph.D.  
Phone: (858) 586-0751  
Email: [ron@rrregs.com](mailto:ron@rrregs.com)  
Drug Proprietary Name: Carbaglu (carglumic acid)  
NME: Yes  
Review Priority: Priority

Study Population includes < 17 years of age: Yes  
Is this for Pediatric Exclusivity: No, Orphan

Proposed New Indication(s): Treatment of Hyperammonemia

PDUFA: 12/18/09  
Action Goal Date: 12/18/09  
Inspection Summary Goal Date: 11/18/09  
Advisory Committee Meeting: We are planning for an advisory committee meeting so inspections must be completed by the Inspection Summary Goal Date.

**Background**

NDA 22-562 is an original new drug application for Carbaglu (carglumic acid) for the treatment of hyperammonemia secondary to N-acetylgulutamase synthase (NAGS) deficiency, a type of metabolic defect in the family of Urea Cycle disorders. Carbaglu was given Orphan Drug designation on January 20, 1998 and Fast Track Designation on May 15, 2007 to IND 61,265. FDA received the last piece of a rolling review application for Carbaglu in July 2008, however, the sponsor withdrew the application in order to avoid a refuse to file action, which would have resulted issues such as incomplete translation of documents in foreign languages, illegible print and nonstandard dataset definitions.

On June 18, 2009, Orphan Europe submitted a new NDA for Carbaglu. The principle study on which the clinical review will be based is a retrospective analysis of 24 patients treated over 15 years at foreign clinical sites. As such, none of the studies were conducted under IND.

See Appendix A for more information on Urea Cycle Disorders and Carbaglu. See Appendix B for more information on alternative treatments (not cures) for hyperammonemia.

**II. Protocol/Site Identification**

*No protocol. This study consists of a retrospective analysis of patients treated with Carbaglu.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Subject ID</b>	<b># of Subjects</b>	<b>Indication</b>
Hopital Debrousse Service de maladies metaboliques et pediatrie genetique 29 Rue Soeur Bouvier 69322 Lyon Cedex France Phone: 011 33 472385722 Fax: 011 33 472385858	(b) (6)	5	Treatment of Hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency)
Groupement Hospitalier Est, Hopital Femme-Mere-Enfant Service des Maladies hereditaires du metabolisme 59 Boulevard Pinel 69677 Bron Cedex France Phone: 011 33 472129537 Fax: 011 33 472129542	(b) (6)	6	Treatment of Hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency)
Klinik fur Kinder und Jugendliche Luisenstrasse 7 D-78461 Konstanz Germany Phone: 011 49 75318012855 Fax: 011 49 75318011667	(b) (6)	2	Treatment of Hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency)

Please note, the two locations in France (Lyon Cedex and Bron Cedex) are very close in proximity and 5 of the 6 French patients were treated at both of the French hospitals.

**III. Site Selection/Rationale**

*The rationale for inspection is as follows:*

- *Carbaglu has been studied solely outside of the United States, therefore all evidence for clinical safety and effectiveness with treatment comes from foreign sites.*
- *It is an New Molecular Entity (NME).*
- *The NDA studies were not conducted under IND.*

*The rationale for the site selection is:*

- *These were the sites with the largest numbers of subjects*

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact Roland Girardet, RPM, at 301-796-3827 or Virginia Elgin, Medical Officer, at 301-796-2319.

Concurrence: (as needed)

Lynne Yao, M.D.

Virginia Elgin, M.D.

Donna Griebel, M.D.

Medical Team Leader

Medical Reviewer

Division Director (for foreign inspection requests or requests for 5 or more sites only)

Should you require any additional information, please contact Roland Girardet, RPM, 301-796-3827 or Virginia Elgin, M.D., Medical Reviewer, 301-796-2319.

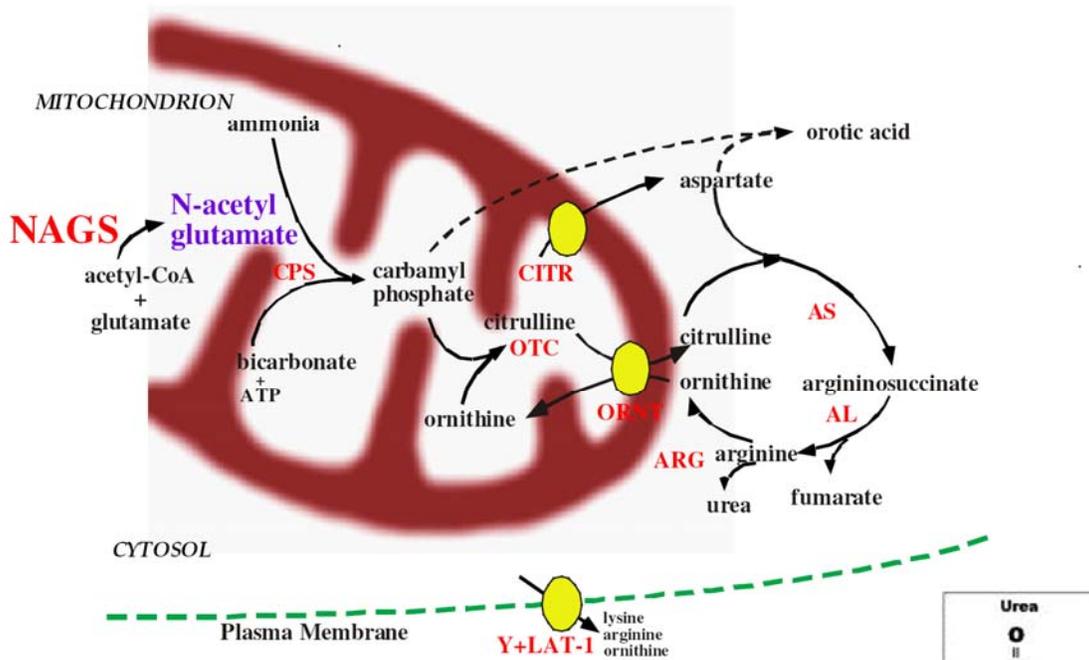
Appendix A. UREA CYCLE DISORDERS AND CARBAGLU FOR NAGS DEFICIENCY

The urea cycle consists of a series of enzymes which function in an interdependent fashion to rid the body of excess nitrogen. If any enzyme in the urea cycle functions abnormally or is absent, hyperammonemia can result which can prove life-threatening to patients with a major enzyme deficiency in the urea cycle. Individuals with urea cycle defects associated with hyperammonemia may suffer from the following:

- Neurocognitive dysfunction including mental retardation and cerebral palsy
- Blindness
- Seizures and epilepsy
- Brain edema that can prove fatal

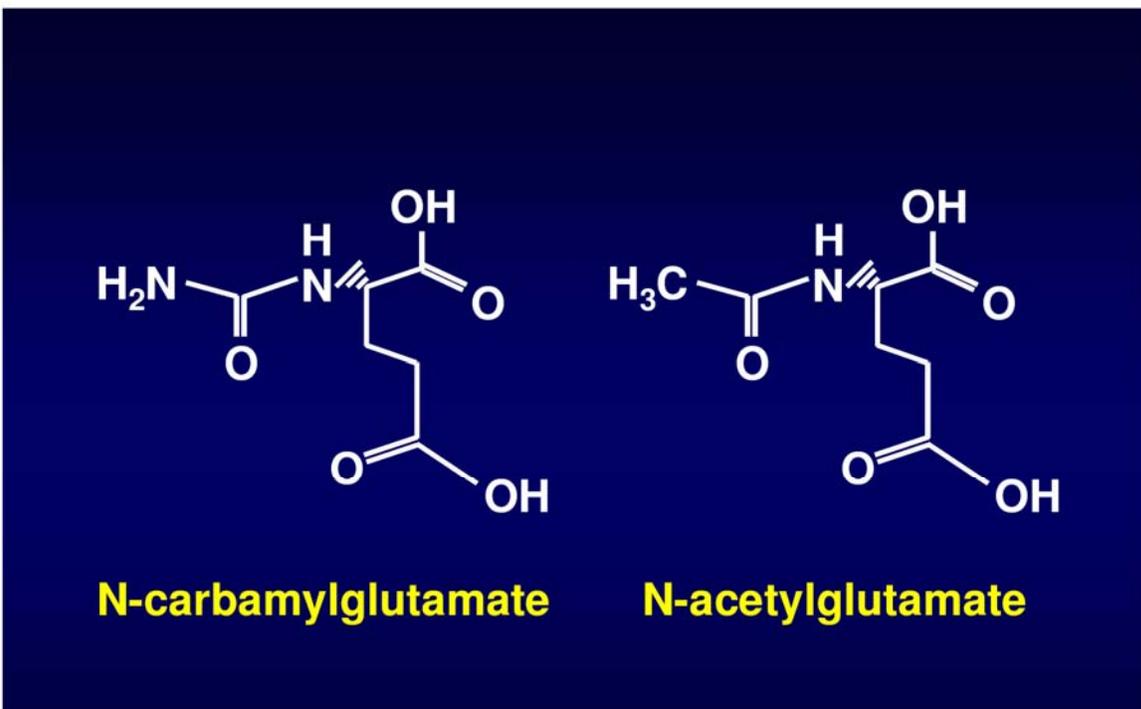
The Figure below illustrates the urea cycle which functions partially in the cell's cytosol and partially within the cell's mitochondria.

### Urea cycle



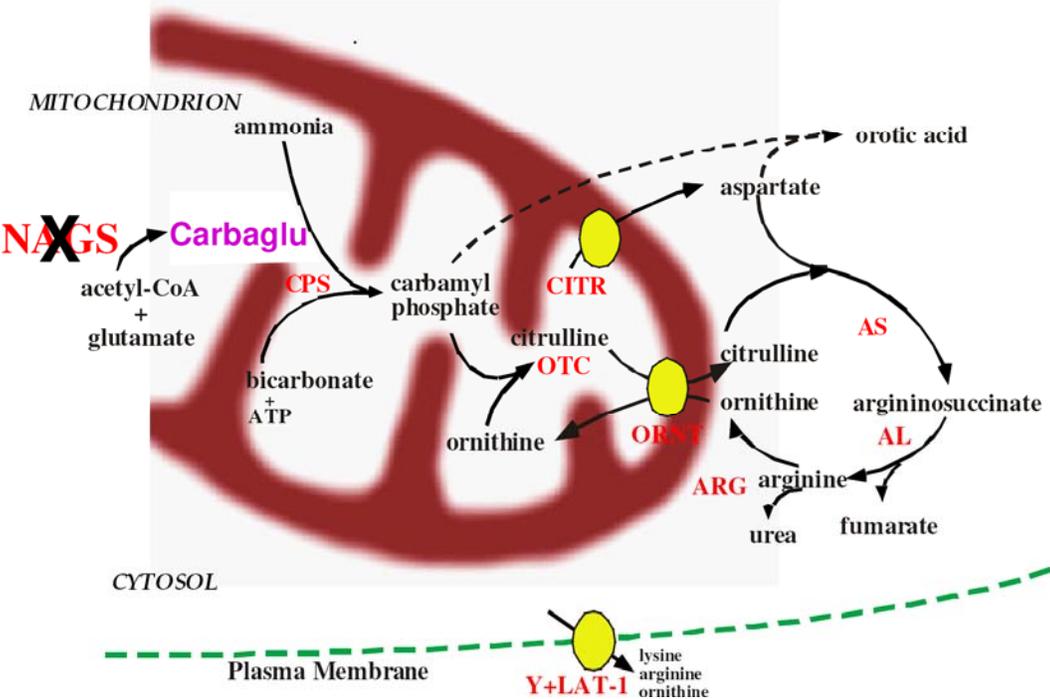
NAGs deficiency is an ultra rare autosomal recessive inherited type of urea cycle defect for which leads to hyperammonemia that can be life threatening. There are an estimated four cases in the United States. This submission covers the treatment of 24 patients throughout Europe over at least a 15 year period, with currently 19 surviving patients. The patients were not studied all concurrently as in a normal clinical trial, so that the information we are reviewing presents in narrative form, like an individual case series.

Carbaglu is a structural analogue of N-acetyl-glutamate synthase normally produced by N-acetyl-glutamate synthase (NAGS). N-acetyl-glutamate activates the first enzyme of the urea cycle essential to the normal function of the urea cycle. The figure below shows the molecular structure of Carbaglu (carglumic acid) compared to it's analogue found in nature, N-acetyl glutamate:



The figure below illustrates where Carbaglu (carglumic acid) plays a role in the urea cycle.

### Carbaglu in NAG deficiency



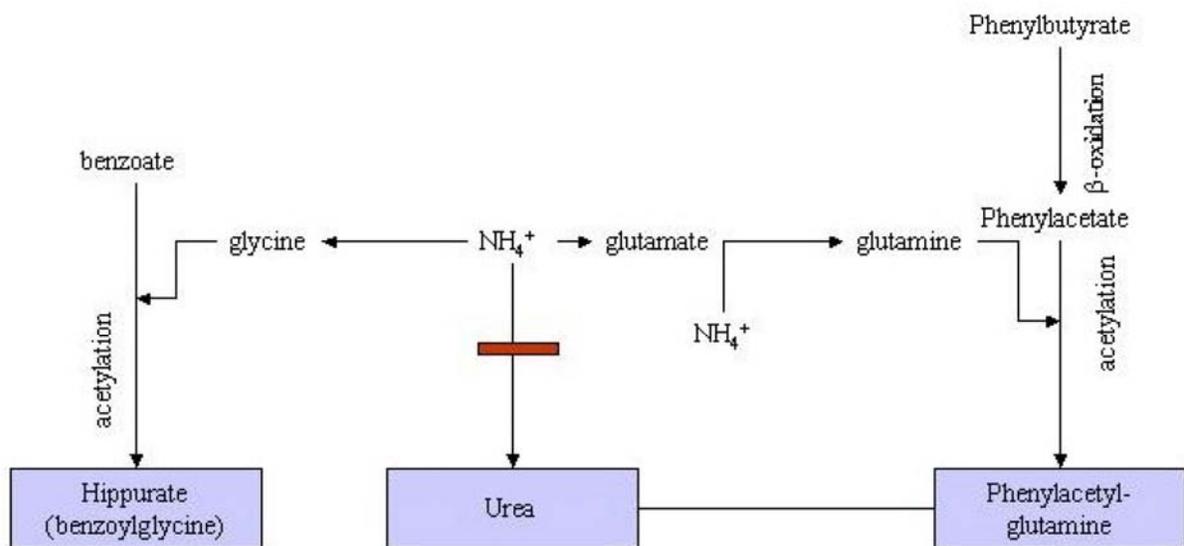
## Appendix B. Alternative Treatments for Hyperammonemia

Alternatives to treat hyperammonemia secondary to NAGS deficiency include the following:

- Nitrogen scavengers such as sodium benzoate, sodium phenylacetate and sodium phenylbutyrate. Sodium benzoate conjugates with glycine and benzoate and is excreted in the urine as hippurate such that one nitrogen atom derived from glycine gets eliminated. It may be used in conjunction with sodium phenylacetate and may also have a synergistic effect with hemodialysis.
- Lactulose as well as hemodialysis can be used in the acute setting to treat hyperammonemia. Lactulose is a disaccharide (fructose and lactulose) that bacterial flora metabolize to form of fatty acids which acidify the colon. This favors the formation of  $\text{NH}_4$  from  $\text{NH}_3$  which reduces  $\text{NH}_3$  absorption and therefore  $\text{NH}_3$  levels
- Arginine and citrulline, depending on the enzymatic defect in the urea cycle, can be
  - Used as a replacement therapy or as a supplemental boost to the urea cycle pathway.
  - Be diet-restricted as in the case of arginase deficiency (arginine) or ornithine transcarbamoylase deficiency (citrulline is a precursor to arginine)
- Carnitine is often added to a patient's therapy because it facilitates activation of mitochondrial oxidative enzymes.
- Protein restriction in a diet that contains essential amino acids (typically 1-1.5 g/day; g/kg)

The figure below illustrates alternative pathways for the treatment of hyperammonemia:

### Alternate Pathway Therapy



Unlike the alternatives above, Carbaglu is designed to correct the metabolic error by providing an analogue substrate which serves as an alternative way of activating CPS I and therefore is designed to treat the cause of the hyperammonemia rather than the hyperammonemia itself.

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/s/

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Virginia E Elgin  
7/15/2009 04:01:51 PM

Anne Pariser  
7/15/2009 04:25:17 PM



NDA 22-562

**NDA ACKNOWLEDGMENT**

Orphan Europe, SARL  
c/o R & R Registrations  
Attention: Ronald G. Loenardi, Ph.D.  
President  
9915 Caminto Chirimolla  
San Diego, CA 92131

Dear Dr. Leonardi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: June 17, 2009

Date of Receipt: June 18, 2009

Our Reference Number: NDA 22-562

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 17, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been

met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: [http://internet-dev.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm). Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-3827.

Sincerely,

*{See appended electronic signature page}*

Roland Girardet, M.H.S., M.S., M.B.A.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Roland Girardet  
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