

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-562

APPROVAL LETTER



NDA 022562

NDA APPROVAL

Orphan Europe, SARL
c/o U.S. Agent, R&R Registrations, Inc.
Attention: Ronald 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 acknowledge receipt of your submissions dated July 13, 2009, July 28, 2009, July 29, 2009, July 30, 2009, August 3, 2009, August 6, 2009, August 11, 2009, August 12, 2009, August 24, 2009, August 31, 2009, September 8, 2009, September 17, 2009, October 5, 2009, October 14, 2009, October 15, 2009, October 20, 2009, October 23, 2009, November 20, 2009, November 24, 2009, December 7, 2009, January 7, 2010, February 7, 2010, February 8, 2010, February 12, 2010, February 16, 2010, February 17, 2010, and February 22, 2010, March 2, 2010, March 4, 2010, March 9, 2010, March 10, 2010, March 15, 2010, March 16, 2010 and March 17, 2010.

This new drug application provides for the use of Carbaglu (carglumic acid) Tablets, 200 mg in pediatric and adult patients as an adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency), and as maintenance therapy for chronic hyperammonemia due to NAGS deficiency.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and with the minor editorial revisions listed below, as agreed upon in your letters dated March 15, 2010 and March 16, 2010:

- Add National Drug Code (NDC) numbers to the package insert and the carton and immediate container labels;
- Add a bar code to the carton and immediate container labels or obtain an exemption from the bar code requirement per 21 CFR 201.25(d); and
- Add distributor information in the appropriate format described in 21 CFR 201.1(h)(5) to the carton and immediate container labels.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert and includes the NDC number. For administrative purposes, please designate this submission, “**SPL for approved NDA 022562.**”

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, and include the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022562.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious

risks of carcinogenicity, or unexpected serious risks related to long-term exposure in patients, including pregnant women and their fetuses.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1604-1. A 2-year carcinogenicity study in a single species.

The timetable you submitted on March 17, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	February 28, 2011
Study Completion Date:	September 30, 2013
Final Report Submission:	September 30, 2014

1604-2. 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.

The timetable you submitted on March 17, 2010 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	January 31, 2011
Study Completion Date:	July 31, 2026
Final Report Submission:	January 31, 2027

1604-3. 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.

The timetable you submitted on March 17, 2010 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	January 31, 2011
Study Completion Date:	July 31, 2026

Final Report Submission: January 31, 2027

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated March 17, 2010. These commitments are listed below.

1604-4. 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: December 31, 2010

1604-5. An *in vitro* study to assess the potential for carglumic acid to inhibit or induce cytochrome P450 enzymes.

Final Protocol Submission: December 31, 2010
Study Completion Date: September 30, 2011
Final Report Submission: March 31, 2012

Submit clinical protocols to your IND 061265 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

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

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Package Insert, Carton and Container Labeling

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

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

/s/

JULIE G BEITZ
03/18/2010