DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22562/S-002

**SUPPLEMENT APPROVAL**

Orphan Europe
c/o Biotech & Pharmaceutical Consulting
Attention: Eric S. Gruff, Ph.D., MBA
U.S. Regulatory Agent
15696 Oakstand Road
Poway, CA 92064

Dear Dr. Gruff:

Please refer to your Supplemental New Drug Application (sNDA) dated April 4, 2013, received April 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Carbaglu (carglumic acid) tablets.

We acknowledge receipt of your amendment dated Aug 1, 2013.

This Prior Approval supplemental new drug application provides for the addition of results from your study report entitled "Evaluation of the potential induction effect of CARBAGLU on CYP1A1/2, CYP2B6 and CY3A4/5 enzymes activities in human hepatocytes" and "Evaluation of the potential inhibition effect of CARBAGLU on cytochrome P450 enzyme activities using pooled human liver microsomes," dated April 5, 2012, in fulfillment of PostMarketing Commitment 1604-5.

The following text was added to Section 12.3 Pharmacokinetics:

Drug Interaction Studies
No drug interaction studies have been performed. Based on in-vitro studies, Carbaglu is not an inducer of CYP1A1/2, CYP2B6, CYP2C, and CYP3A4/5 enzymes and not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

**REPORTING REQUIREMENTS**

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

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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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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JOYCE A KORVICK
08/05/2013