

NDA 022562/S-008 & 009

## SUPPLEMENT APPROVAL

Recordati Rare Diseases  
Attention: Sandy S. Suh, Pharm.D.  
VP, Regulatory Affairs & Chief Compliance Officer  
100 Corporate Drive  
Lebanon, NJ 08833

Dear Dr. Suh:

Please refer to your supplemental new drug applications (sNDAs) dated and received November 30, 2018, and your amendments, 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 April 24, 2020, which constituted a complete response to our May 30, 2019, action letter.

We acknowledge receipt of your major amendment dated October 9, 2020, which extended the goal date by three months.

These Prior Approval supplemental new drug applications provide for a new indication for use as an adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia or methylmalonic acidemia.

### **APPROVAL & LABELING**

We have completed our review of these applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with the minor editorial revision listed below and reflected in the enclosed labeling.

- The heading for Table 3 of the Prescribing Information was **bolded**.

### **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 FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use), 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.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

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|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PMC 4009-1 | Collect data on biochemical effects, clinical outcomes, and serious safety events associated with the short-term and long-term use of Carbaglu in pediatric and adult patients with propionic acidemia (PA) or methylmalonic acidemia (MMA), including data on pregnancy and fetal outcomes. This data collection may be performed as part of an existing study or registry. Specifically, assess plasma ammonia and related metabolites, short-term and long-term clinical outcomes, serious adverse events, risks of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant (through the first year of life) with exposure to Carbaglu over short- |
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<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

term and long-term treatment. This collection of data should span at least 10 years.

The timetable you submitted by email on January 19, 2021 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2021  
Study/Trial Completion: 03/2032  
Final Report Submission 09/2032

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>3</sup>

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup>

## **REPORTING REQUIREMENTS**

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

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<sup>3</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, contact Nicolas Kong, Regulatory Project Manager at [Nicolas.Kong@fda.hhs.gov](mailto:Nicolas.Kong@fda.hhs.gov) or 240-402-0269.

Sincerely,

*{See appended electronic signature page}*

Patroula Smpokou, M.D.  
Deputy Director  
Division of Rare Diseases and Medical  
Genetics (DRDMG)  
Office of Rare Diseases, Pediatrics, Urologic  
and Reproductive Medicine (ORPUM)  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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NICOLAS KONG  
01/22/2021 05:11:24 PM

PATROULA I SMPOKOU  
01/22/2021 05:13:41 PM