NDA 209377/S-003

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

American Regent, Inc.
Attention: Elizabeth Ernst,
Global Executive Director of Regulatory Affairs
6610 New Albany Road East
New Albany, OH 43054

Dear Ms. Ernst,

Please refer to your supplemental new drug application (sNDA) dated and received April 28, 2020, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zinc Sulfate Injection, 3mg/mL, 5mg/mL, and 1mg/mL.

This "Changes Being Effected" supplemental new drug application provides for revisions to stability and storage information in the Dosage and Administration section of the Prescribing Information (PI) to extend storage of the drug product under refrigeration after admixing to up to 9 days.

APPROVAL & LABELING

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 with minor editorial revisions reflected in the enclosed labeling.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] 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.

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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling **or** carton and container labeling submitted on October 9, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209377/S-003**." Approval of this submission by FDA is not required before the labeling is used.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We also refer to your sNDA, S-002, received on December 20, 2019, and your general correspondence received on September 9, 2020, stating that the addition of the new strength approved in S-002 was intended to fulfill the following postmarketing requirement listed in the July 18, 2019, approval letter.

3663-1 Develop an age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 12 kg

We have reviewed your submission and conclude that the above requirement was fulfilled.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

Since Zinc Sulfate Injection was approved on July 18, 2019, we have become aware that the originally approved strengths (3 mg/mL, 5 mg/mL) and the recently approved strength (1 mg/mL) were not tested for the potential elemental impurities (b) (4) (b) (4) during the development of the product. The absence of drug product testing for these elemental impurities raises a safety concern because these elements may be used as supplements in total parenteral nutrition (TPN), and excessive exposure to (b) (4) may be associated with organ toxicity (e.g., bone, thyroid), particularly in neonates. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of organ toxicity (e.g., bone, thyroid) in all strengths of Zinc Sulfate Injection.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

3663-2 Conduct a study to determine the levels of the potential elemental impurities (b) (4) in at least three batches of Zinc Sulfate Injection, in each of the following strengths: 30 mg/10 mL (3 mg/mL), 25 mg/5 mL (5 mg/mL), and 10 mg/10 mL (1 mg/mL).

Safety assessment of the potential exposure (b) (4) needs to be based on the administration of 0.4, 0.133, and 0.08 mL/kg/day of the 1 mg/mL, 3 mg/mL, and 5 mg/mL strengths, respectively, of Zinc Sulfate Injection in preterm neonates less than 3 kg, in accordance with dosing recommendations. In keeping with the Division of Hepatology and Nutrition's recommended approach for controlling (b) (4) levels, you should use a maximum acceptable dose of (b) (4) mcg/kg/day (b) (4) and (b) (4) mcg/kg/day (b) (4) to calculate an acceptance criterion and a control threshold ((b) (4) times the acceptance criterion) for these elements in each product strength. If (b) (4) (b) (4) are known to be potential leachables in the container closure system, then measurement of these elements should be done at the end of the product shelf life.

The timetable you submitted on October 27, 2020 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2021
Study Completion:	04/2021
Final Report Submission:	05/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission 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.

REPORTING REQUIREMENTS

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

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Thao Vu, Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Carton and Container Labels

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.

/s/

JUDITH A RACOOSIN
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