DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021703/S-017
NDA 207026/S-002

SUPPLEMENT APPROVAL

Baxter Healthcare Corporation
Attention: Kristin Henney
Associate Director, Regulatory Affairs
32650 N. Wilson Road
WG1-3
Round Lake, Illinois 60073

Dear Ms. Henney:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prismasol Renal Replacement Solution (NDA 021703) and Phoxillum Renal Replacement Solution (NDA 207026).

We acknowledge receipt of your amendment dated July 7, 2016

This supplemental new drug application provides for the following changes to labeling (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text:

1. In **HIGHLIGHTS**, the following text was changed:

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2, 2.3)	12/2015
Contraindications	07/2016
Warnings and Precautions (5.1)	07/2016

----------CONTRAINDICATIONS----------

- Known hypersensitivities to PRISMASOL and PHOXILLUM solutions ~~None~~(4)

---------- WARNINGS AND PRECAUTIONS----------

- Monitor ~~H~~hemodynamic status and fluid inputs and outputs, potassium, phosphorous, other electrolytes and acid-base balance ~~should be monitored~~. Abnormalities may be corrected by the use of appropriate formulations and dosage of PRISMASOL and PHOXILLUM solutions (5.~~3~~1)
- Antidiabetic therapy may need adjustment during treatment with dextrose containing formulations (5.~~4~~2)

2. Under **DOSAGE AND ADMINISTRATION**, the following text was added after Table 1:

~~Select t~~The mode of therapy, solute formulation, flow rates, and length of PRISMASOL and PHOXILLUM replacement therapy in CRRT should be established by a physician based on the patient's clinical condition, blood concentration of phosphate and ~~fluid~~other electrolytes, acid-base and glucose balance. Administer either PRISMASOL or PHOXILLUM into the extracorporeal circuit:

- Before (pre-dilution) the hemofilter or hemodiafilter,
- After (post-dilution) the hemofilter or hemodiafilter, or
- Before and after the hemofilter or hemodiafilter.

2.3 Preparing the Solution
Use only if the overwrap is not damaged, all seals are intact, frangible pin or peel seal is not broken, and the solution is clear. ~~Press bag firmly to test for any leakage. Do not use if container is damaged or leaking.~~

The solution may be ~~heated to no more than~~warmed to ~~40~~ 37°C/~~104~~98.6°F inside of the overwrap to enhance patient comfort. However, only dry heat should be used. Solutions should not be heated in water or in a microwave oven. After heating, verify that the solution remains clear and contains no particulate matter.

2.4 Adding Drugs to the Solutions
After mixing, additional drugs may be added to the bag via injection connector (spike connector) in large compartment B. In general, drugs other than phosphate should be administered through a different access line.

When introducing ~~additives~~ drugs, use aseptic techniques and mix thoroughly. Do not use if there is a color change and/or the appearance of precipitates, insoluble complexes or crystals after addition of medication.

3. The text "After removing the overwrap, inspect the container for leakage by pressing firmly on the bag. Discard the bag if any leakage is detected since sterility cannot be assured." was added to **Step 1** in **Figure 2** and **Step 1** in **Figure 7**.

4. Under **CONTRAINDICATIONS**, the following text was added/deleted:

~~None~~ PHOXILLUM and PRISMASOL replacement solutions are contraindicated in patients with known hypersensitivities to these products.

5. Under **WARNINGS AND PRECAUTIONS**, the section was re-numbered and the following text was added/deleted:

5.1 Electrolyte and Volume Abnormalities
~~Monitor hemodynamic status and fluid, electrolyte and acid-base balance throughout the procedure.~~ PHOXILLUM and PRISMASOL solutions can affect electrolytes and volume and may result in hyperkalemia or hyperphosphatemia. Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorous, other electrolytes and acid-base balance throughout the procedure. Abnormalities may be corrected by changing the

formulation of replacement solution and/or dialysate, supplementation, or adjusting flow rates appropriately [*see Dosage and Administration (2)*].

PHOXILLUM replacement solutions contain hydrogen phosphate, a weak acid that may increase the risk of metabolic acidosis.

~~During hemofiltration or hemodiafiltration using PRISMASOL or PHOXILLUM replacement solutions, abnormalities in the plasma concentration of potassium, calcium, magnesium, and phosphate may develop. These abnormalities may be corrected by changing the formulations of replacement solution or by supplementation *[see Dosage and Administration (2)]*.~~

6. Under **ADVERSE REACTIONS**, the following section as added:

6 ADVERSE REACTIONS

The following adverse reactions have been identified with other similar products and therefore, may occur with use of these products:

- Metabolic acidosis
- Hypotension
- Acid-base disorders
- Electrolyte imbalance
- Hyperphosphatemia (for phosphate containing solutions)
- Fluid imbalance

7. Under **DRUG INTERACTIONS**, the following text was added/deleted:

As with the use of other replacement solutions, blood concentrations of dialyzable drugs may be ~~influenced~~ reduced by CRRT due to their removal by the hemofilter or hemodiafilter. The blood concentrations of certain drugs may need to be monitored and appropriate therapy implemented to correct for removal during treatment.

8. The revision date and version number were updated.

There are no other changes from the last approved package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended, and 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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, please call:

Lori Anne Wachter RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
07/20/2016