CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207026Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	05-January-2015
From	Mohan Sapru, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	207026
Type of Application	505(b)(2)
Applicant	Gambro Lundia AB
Date of Receipt	13-March-2014
PDUFA Goal Date	13-January-2015
Proposed Proprietary Name	Phoxillum
Dosage forms / Strength	Sterile Solutions, BK4/2.5 and B22K4/0
Route of Administration	Extracorporeal Circuit
Proposed Indication(s)	Replacement Solution in Patients Undergoing Continuous Renal Replacement Therapy (CRRT)
Recommended:	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- CMC (Sherita D. McLamore-Hines, Ph.D.); in DARRTS, dated 12-Nov-2014
- Microbiology (Denise Miller); in DARRTS, dated 12-Nov-2014
- Manufacturing Facilities (Vibhakar Shah, Ph.D.); in PANORAMA, dated 18-Dec-2014
- Final CMC Approval Recommendation Memo (Olen Stephens, Ph.D.); in PANORAMA, dated 18-Dec-2014
- Clinical (Shen Xiao, M.D., Ph.D.); in DARRTS, dated 19-Dec-2014
- DMEPA (Grace P. Jones, Pharm.D., BCPS); in DARRTS, dated 09-October-2014
- Quality Biopharmaceutics (Okpo Eradiri, Ph.D.); in DARRTS, dated 29-April -2014

1. Introduction

The applicant, Gambro Lundia AB, has sought U.S. marketing approval for Phoxillum under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR §314.54. The applicant proposes to use two different pre-packaged sterile solutions of Phoxillum for use as replacement solutions in hemofiltration and hemodiafiltration procedures during continuous renal replacement therapy (CRRT). CRRT, a short-term treatment, is considered as a life-saving technique that is used in intensive care setting.

2. Background

The proposed Phoxillum solutions (BK4/2.5 and BK22K4/0) that contain sodium, potassium, magnesium, chloride, phosphate, and bicarbonate with or without calcium, have been formulated for use as replacement solution in patients undergoing continuous renal replacement therapy. These solutions are considered to be dosages of the same drug with the same active moiety or principal structural features. The current application relies on the Agency's determination of safety and efficacy for PrismaSol solutions, which have been previously approved for marketing under NDA 21703 on October 25, 2006.

3. Chemistry, Manufacturing and Controls (CMC)

Drug Substances: The drug substances present in Phoxillum solutions include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium bicarbonate, and dibasic sodium phosphate. The drug master files (DMFs) for (b) (4) have been reviewed by CMC reviewer and have been found to be adequate to support the approval of this NDA.

Drug Product: Phoxillum solutions are filled in a two-compartment bag, a small compartment containing the electrolyte solution and a large compartment containing the buffer solution. One red frangible pin is located between the two compartments which is broken immediately prior to use to mix the contents of the two compartments, which results in formulation of the final reconstituted solution for patient use. The applicant refers to these two presentations as BK 4/2.5 and B22K4/0. The small compartment contains calcium chloride and magnesium chloride whereas the large compartment contains sodium chloride, sodium bicarbonate, potassium chloride and dibasic sodium phosphate with water for injection to obtain the desired volume. Hydrochloric acid is used (b) (4) (b) (4) to adjust pH (b) (4) n and carbon dioxide is used for the same purpose (b) (4). (b) (4)

The container closure system is a two compartment PVC bag, (b) (4)

Per CMC review (in DARRTS, dated 12-Nov-2014), the reviewer recommended approval from a CMC perspective pending an "acceptable" recommendation from the Office of Compliance for manufacturing facilities.

Manufacturing Facilities Review/Inspection: Per facilities status communication in PANORAMA, dated 18-Dec-2014, the Office of Compliance (OC) issued an overall "Acceptable" recommendation for all manufacturing facilities supporting the NDA 207026 for Phoxillum BK 4/2.5 and B22K4/0 solutions.

Final CMC Approval Recommendation: Pursuant the overall "Acceptable" recommendation for all manufacturing facilities by OC, the quality review team per memo by Dr. Olen Stephens (in PANORAMA, dated 18-Dec-2014) recommended approval for this NDA from CMC perspective.

4. Product Quality Microbiology

The proposed product is [redacted] (b) (4) The product risk is minimized though the validation of the [redacted] (b) (4) . The reconstituted solution is for single use only. The microbiology reviewer has recommended approval from a quality microbiology perspective.

5. Biopharmaceutics

Per ONDQA filing review (in DARRTS, dated 4/29/14), the Biopharmaceutics reviewer concluded that there are no Biopharmaceutics review issues pertinent to this NDA, and hence, no further action is warranted from Biopharmaceutics.

6. Clinical Pharmacology

N/A

7. Non-Clinical Pharmacology/Toxicology

N/A

8. Clinical/Statistical-Efficacy

N/A

9. Safety

N/A

10. Advisory Committee Meeting

N/A

11. Pediatrics

N/A

12. Other Relevant Regulatory Issues

N/A

13. Labeling

Based on CMC review team's recommendation, the use of (b) (4) on container labels and the Prescribing Information (PI) is not acceptable and should be revised according to current labeling policy**.** The Division of Medication Error Prevention and Analysis (DMEPA) reviewer concluded that PI information is acceptable from a medication error perspective, but has recommended that the container labels and carton labeling be improved to increase the prominence and readability of important information to promote the safe use of this product. The applicant has proposed revisions to the drug label related to the risk of (b) (4). Per clinical reviewer memo (in DARRTS, dated 19-Dec-2014), from a clinical perspective, the proposed labeling language pertaining to these risks is acceptable. In summary, at this stage, a few labeling issues are still pending but these are not expected to impact the approvability of this NDA.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

All the reviews of this application recommended approval, and I concur with the reviewers. Based on the CMC review, an expiry period of 12 months is granted for Phoxillum solutions (BK4/2.5 and BK22K4/0) when stored at room temperature using the applicant's proposed container/closure system. For the reconstituted solution, an expiry period of 24 hours is granted based on applicant's in-use stability data. The clinical review team has sought further clarifications from the applicant to better understand the ability of Phoxillum to contribute to metabolic acidosis in patients on CRRT. Currently, discussion is underway with the applicant to address this issue (b) (4)

- **Risk Benefit Assessment**

Phoxillum solution is a pharmacologically inactive solution. The electrolyte concentrations in the Phoxillum solutions are chosen to restore plasma levels to clinically desired concentrations or maintain plasma levels at the desired concentrations. Importantly, the current NDA is a 505(b)(2) application for use of Phoxillum solutions and relies on the safety and efficacy established for the marketed product PrismaSol solutions (NDA 21703). Consequently, the risk/benefit with Phoxillum solutions is expected to be similar to that for currently marketed PrismaSol solutions.

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/s/

MOHAN K SAPRU
01/08/2015