CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207026Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 13, 2015

To: Anna Park
Regulatory Project Manager
Division of Cardiology and Renal Products (DCRP)

From: Puja Shah
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207026
(Phoxillum) Bk 4/2.5 And B22k4/0

As requested in DCRP's consult dated August 11, 2014, OPDP has reviewed the draft PI and proposed carton/container labeling for PRIMASOL solutions for hemofiltration or hemodiafiltration use, and PHOXILLUM solutions, for hemofiltration or hemodiafiltration use. OPDP reviewed the proposed substantially complete version of the draft PI received via email from DCRP on January 7, 2015. Our comments on the draft PI are included directly on the attached copy of the labeling.

OPDP has also reviewed the following proposed carton and container labeling received via email from DCRP on January 7, 2015:

- "draft-carton-container-labels-b22k40bag.pdf"
- "draft-carton-container-labels-b22k40boxlab.pdf"
- "draft-carton-container-labels-bk425bag.pdf"
- "draft-carton-container-labels-2pt5carton.pdf"
- "draft-carton-container-labels-bk425boxlabel.pdf"

OPDP has no comments on the proposed carton and container labeling at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

PUJA J SHAH
01/13/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 207026</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name: Phoxillum
Established/Proper Name: N/A
Dosage Form: for hemofiltration or hemodiafiltration use
Strengths: BK4/2.5, B22K4/0</td></tr>
<tr><td colspan="3">Applicant: Gambro Lundia AB
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: 03/13/14
Date of Receipt: 03/13/14
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 01/13/15</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: 05/23/14</td><td>Date of Filing Meeting: 04/24/14</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☒ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): As a replacement solution in Continuous Renal Replacement Therapy (CRRT)</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		No clinical studies were conducted.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 24, 2014

BACKGROUND: On March 13, 2014, the applicant submitted their NDA for Phoxillum (BK4/2.5 and B22K4/0). Based on the comparative electrolyte concentrations to the already approved PrismaSol Solutions under NDA 21703, the applicant will cross reference the clinical and nonclinical portions of the NDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anna Park	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Kasturi Srinivasachar		Y
Division Director/Deputy	Norman Stockbridge		Y
Office Director/Deputy	Stephen Grant		N
Clinical	Reviewer:	Shen Xiao	Y
	TL:	Aliza Thompson	N
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	N/A	No clinical studies were submitted
	TL:		
Biostatistics	Reviewer:	N/A	No clinical studies were submitted
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	N/A	No clinical studies were submitted
	TL:	N/A	
Statistics (carcinogenicity)	Reviewer:	N/A	No clinical studies were submitted
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sherita McLamore	Y
	TL:		
Biopharmaceutics	Reviewer	Okpo Eradiri	Y
	TL:		
Quality Microbiology	Reviewer:	Denise Miller	Y
	TL:		
CMC Labeling Review	Reviewer:	Sherita McLamore	Y
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Jean Olumba	N
	TL:	Lisa Khosla	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Amy Chen Karen Bengston		Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: No clinical studies were submitted	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**: No clinical studies were submitted	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments: No clinical studies were submitted	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No clinical studies were submitted	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No clinical studies were submitted	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge M.D., Ph.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 08/14/14

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

ANNA J PARK
01/07/2015

RHPM NDA Overview
06 January 2015

Application:	**NDA 207026** - Phoxillum (BK4/2.5 and B22 4/0) solutions
Sponsor:	Gambro Lundia AB
Classification:	5/S
Indication:	As a replacement solution in Continuous Renal Replacement Therapy (CRRT)
Date of Application:	03 March 2015
Goal Date:	13 January 2015

Background:

The Phoxillum product consists of two different pre-packaged sterile solutions for use as replacement solutions in hemofiltration and hemodiafiltration procedures during continuous renal replacement therapies (CRRT). Phoxillum replacement solutions are supplied in a two-compartment bag with a small and a large compartment. The solutions contained in the small compartment A (electrolyte solution) and in the large compartment B (buffer solution) are sterile solutions and must be mixed immediately prior to use.

Since the proposed concentration of sodium, potassium, calcium, magnesium, chloride and bicarbonate in Phoxillum solutions are well within those already approved for PrismaSol solutions, Gambro is cross referencing the registration of Phoxillum solutions to the already registered PrismaSol NDA 21-703 approved on October 25, 2006. Modules 4 and 5 from PrismaSol's NDA 21-703 already approved are used a reference to support the clinical and non-clinical data required as part of Phoxillum NDA.

The applicant submitted an Orphan Drug Designation Request (#12-3820) on November 25, 2013 and the request was approved on February 14, 2014.

Since the applicant has an approved, marketed NDA for Primasol, which currently covers 7 different Primasol replacement solutions, each with a slight variation in electrolyte ingredients from the others, other than the fact that the new product contains phosphate and the others don't, the Division noted no difference between the product under the new NDA and the approved Primasol solutions (same directions for use, same storage instructions, etc.). Thus, the Division proposed redesignating the pending original NDA as a supplement to the Primasol NDA and have a single label. A teleconference was held with the applicant on August 28, 2014 and the applicant chose to maintain the Phoxillum trade name with separate labeling.

A second teleconference was held on September 8, 2014 and the applicant agreed to combine both PrismaSol and Phoxillum package leaflets into one, while maintaining both Prismasol and Phoxillum as separate tradenames.

On October 2014, the applicant notified us of three European case reports related to acidosis wile on CRRT with Phoxillum, which is currently marked in Europe, and how (b) (4) (b) (4) The Division requested the official case reports be submitted officially to the NDA (received 24 December 2014) and for the applicant to provide their assessment of these cases. If they felt further changes to the label were necessary because of these cases, the applicant should propose the revised text and submit this information by November 20, 2014. The cases were received and reviewed and an additional information request was made on January 2, 2015 regarding the ability of Phoxillum to contribute to metabolic acidosis in patients on CRRT. The information was received on January 9, 2015 and the Division concluded there was nothing among the PHOXILLUM variations that would make patients more vulnerable to metabolic acidosis.

Reviews: *(Please note these are summaries and not complete reviews. Please refer to their complete reviews in DARRTS).*

Division Director's Memo *(12 January 2015)*
Reviewer: Norman Stockbridge, M.D., Ph.D.

Conclusion: Approval

Summary:
Although products are different for User Fee purposes if they contain distinct sets of ingredients, as Dr. Sapru points out, the Division treats physiological saline solutions as a single product. Where variations lie largely within physiological bounds for the electrolyte constituents, the Division has not asked for clinical data for novel variations.

The two PHOXILLUM products extend the set of Gambro products from 8 to 10, but we thought, and the sponsor agreed, that all ten products ought to be described in a single label. The first 8 variations are marketed under the name PRISMASOL. The sponsor requested to retain the PHOXILLUM name for these two new phosphate-containing variations, and I concurred; this decision results in what may be a label unique with two trade names.

There was considerable discussion regarding the classification in the label. After input from DMEPA and USP, we settled on "renal replacement solution", but I note that, perhaps unlike many products, you cannot use the classification to tell you what is potentially substitutable.

Dosing instructions for these products deal with the physical container and allowable additions, but they are silent on selection of a particular variation for a patient. Nephrologists are supposed to know what they want to accomplish. This aspect of labeling is not different with the addition of PHOXILLUM.

Late in the review, the Division became aware of several cases of metabolic acidosis on PHOXILLUM, and a question has arisen about the total buffering capacity of the variations of PRISMASOL and PHOXILLUM. The sponsor provided these data on 9 January 2015, and there only minor differences in buffering capacity among the ten variations in this product line. I conclude that there is nothing among the PHOXILLUM variations that make patients more vulnerable to metabolic acidosis.

CDTL (08 January 2015)

Reviewer: Mohan Sapru, M.D.

Conclusion: Approval

Labeling:

Based on CMC review team's recommendation, the use of [redacted] (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 [redacted] (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.

Summary:

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 [redacted] (b) (4)

Clinical Memo (19December 2014)

Reviewer: Shen Xiao, M.D.

A clinical review was not conducted as the applicant did not submit any clinical data with their NDA application. However, a review was conducted on the applicant's proposed revisions to the drug label (b) (4) (b) (4) (email correspondence to Anna Park dated November 20, 2014).

Labeling:
Proposed revisions to the drug label (submission dated November 20, 2014):

(b) (4)

Cases of metabolic acidosis: The submitted narratives, which are appended to this review, contain limited information on these cases. According to the submitted information, in all three cases: (1) the patient was acidotic at baseline; (2) the patient was treated with hemodiafiltration and Phoxilium was used as both the replacement and dialysis solution; (3) the acidosis worsened during treatment with Phoxilium and improved after " dialysis was turned off" and/or the patient was switched from Phoxilium to Prismasol.

Reviewer's comment: Although there were likely multiple factors contributing to the acidosis in the cases reported in Europe, the reported improvement in acidosis after switching to Prismasol and/or after stopping dialysis, suggests that use of Phoxilium as a dialysis and replacement solution may have played a role.

Applicant's rationale for the proposed changes:

1. Metabolic acidosis: Metabolic acidosis is common in patients with renal failure requiring CRRT and can result from the kidney's reduced ability to excrete hydrogen ions, an increased rate of hydrogen ion generation as a result of hypercatabolism, and/or lactic acidosis (especially in patients with sepsis and

multi-organ failure). Since phosphate is weakly acidic, replacement solutions containing phosphate, such as Phoxilium and Phoxillum, could contribute to metabolic acidosis in some patients on CRRT. The applicant also notes that the bicarbonate concentration of Phoxillum (32 mmol/L in the BK4/2.5 formulation and 22 mmol/L in the B22K4/0 formulation) is somewhat lower than the effective bicarbonate concentration of most other CRRT therapeutic fluids (typically 35 mmol/L). Thus, in comparison to most CRRT therapeutic fluids, including the approved product, Prismasol, Phoxillum has slightly less buffering capacity and a relative acidifying effect.

In addition to providing the narratives for the three case reports, the applicant reports the findings in two different publications by Chua and colleagues. These publications describe acid/base parameters over a 42-hour period in the same group of 15 CRRT patients treated with Phoxilium as replacement fluid (patients were on CVVH only, without dialysis). In one report, the median serum bicarbonate concentration decreased from 24 mmol/L at CRRT initiation to 20 mmol/L by 42 hours. In the other report, the control CRRT group (N=15) was treated with a replacement fluid (Hemosol B0) that had an effective bicarbonate concentration of 35 mmol/L. In the control group, the median bicarbonate concentration increased from 24 mmol/L to 26 mmol/L over the same time period.

Reviewer's comment:

1. *While patients were receiving Phoxilium as a dialysis and replacement solution in the cases reported in Europe, in the paper(s) published by Chua et al, Phoxilium was used only as a replacement solution (the proposed use for Phoxillum under NDA 207-026).*
2. *Based on the cases to date and the other information provided by the applicant, I agree with the applicant that labeling should emphasize the need for regular monitoring of* (b) (4) *acid/base parameters,* (b) (4)

2. Hyperphosphatemia: Hyperphosphatemia is largely due to reduced renal excretion in patients with acute kidney injury (AKI) and CRRT can effectively and relatively rapidly reduce serum phosphate concentrations by removal in the effluent. As noted by the applicant, if phosphate supplementation is not provided, many patients develop hypophosphatemia during CRRT within the first few days of therapy, hence providing the rationale for a replacement solution such as Phoxillum, which contains phosphate. Nevertheless, there are other sources of phosphate which can increase serum phosphate concentrations in patients with CRRT. For example, in some patients with AKI, hypercatabolism caused by sepsis, trauma or other severe conditions can lead to an increase in the serum level of phosphate. In addition, because of variable CRRT delivery (related to interruptions in therapy or declining CRRT filter performance), the effect of CRRT on serum phosphate concentrations is difficult to predict. For these

reasons, the applicant believes that the label should [redacted] (b) (4)

Reviewer's comment: I agree.

Reviewer's Conclusion: From a clinical perspective, the proposed labeling language pertaining to these risks is acceptable.

Product Quality (12 November 2014)

Reviewer: Sherita McLamore-Hines, Ph.D.

Conclusion: Approval

Labeling:

[redacted] (b) (4) Our current labeling policy is to either omit this language or replace it with a statement such as, "Not made with natural rubber latex" if that statement is true for all materials used in the manufacture of your medical product and container.

Summary:

The application is recommended for "Approval" from CMC perspective.

From a CMC perspective, this application is recommended for approval pending an acceptable recommendation from the Office of Compliance. The drug substances were determined to be safe, effective, and manufactured in a consistent manner with inherent quality in the respective DMFs and in this application. The sponsor identified CQA and established controls to ensure the quality of the drug product. The results of the batch analyses confirm quality of the drug product at release. The intended commercial packaging presentations has been previously used in approved products provide adequate protection of the drug product and ensure drug product quality over the proposed 12-month shelf-life as demonstrated through the drug product stability data. With the exception of the [redacted] (b) (4) statement, the draft labels and package insert are acceptable from a CMC perspective.

Product Quality Microbiology (12 November 2014)

Reviewer: Denise Miller, Ph.D.

Conclusion: Approval

Labeling: Please refer to her review in Panorama.

Summary:

The application is recommended for "Approval".

Division of Medication Error and Prevention (09 October 2014)

Reviewer: Grace P. Jones, Pharm.D., BCPS

Labeling: Please refer Dr. Jones' review in DARRTS. The applicant updated the label incorporating all their recommendations.

Action:

An Approval Letter has been drafted and will be signed by Dr. Stockbridge.

Anna Park
Senior Regulatory Management Officer
January 12, 2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 9, 2014
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 207026
Product Name and Strength:	Phoxillum B22K4/0, and Phoxillum BK4/2.5 Hemofiltration and Hemodiafiltration Solution
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gambro Lundia AB
Submission Date:	July 23, 2014
OSE RCM #:	2014-573
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed Phoxillum B22K4/0 and Phoxillum BK4/2.5 container labels, carton labeling, and Prescriber Information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

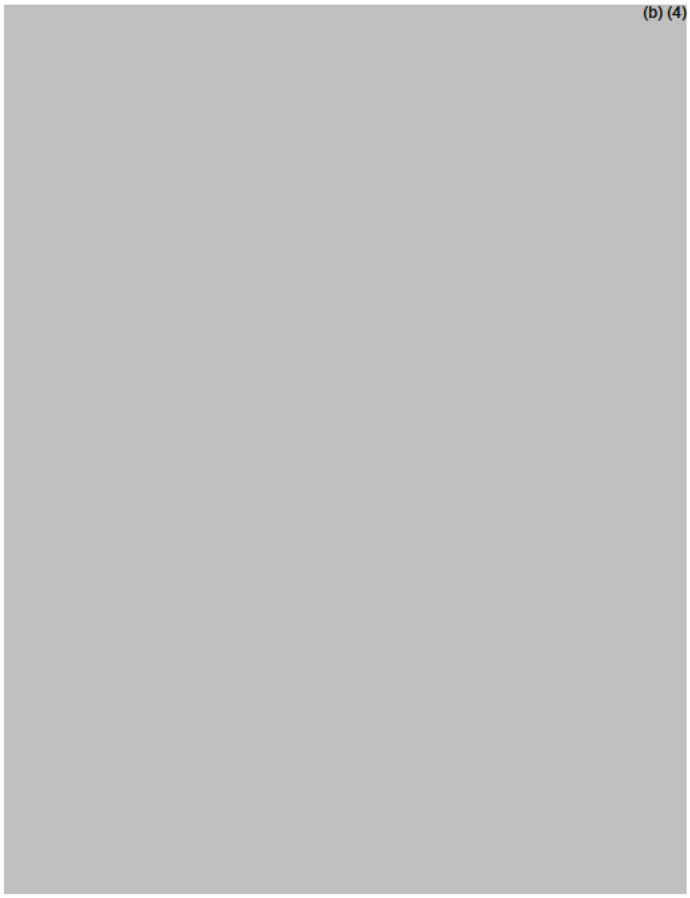
N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant cross-referenced their current product PrismaSol (NDA 021703) in the July 23, 2014 submission for Phoxillum B22K4/0 and Phoxillum BK4/2.5, and indicated that the two products are packaged in the same manner. Therefore, we searched for post-marketing medication error reports associated with PrismaSol, but retrieved zero cases. However, our review of the current PrismaSol container labels found that PrismaSol contains an extra label that identifies and provides mixing instructions for small compartment A with the large compartment B (See Figure 1) (b) (4) .

We provide recommendations for the proposed Phoxillum B22K4/0 and Phoxillum BK4/2.5 container labels to identify and to improve instructions for mixing the two compartments that must be mixed prior to use.

Figure 1. PrismaSol Container Label (NDA 021703 Annual Report-10, submitted 12/16/2013)



4 CONCLUSIONS & RECOMMENDATIONS

We conclude the proposed Prescriber Information is acceptable from a medication error perspective, but proposed container labels and carton labeling can be improved to increase the prominence and readability of important information to promote the safe use of this product. We recommend the following be implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR GAMBRO

A. Container Labels

1. The proposed container labels for Phoxillum B22K4/0 and Phoxillum BK4/2.5 (b) (4) We recommend adding an extra container label to Phoxillum B22K4/0 and Phoxillum BK4/2.5 bags to provide such identification and mixing instruction that is similar to your PrismaSol products:

Additionally, to clarify the mixing instructions, we recommend revising the mixing instruction statement from [redacted] (b) (4) to "BREAK red pin and MIX compartment A with compartment B" (or similar language).

2. The proposed container labels for Phoxillum B22K4/0 and Phoxillum BK4/2.5 [redacted] (b) (4) We recommend adding a similar graphic "Compartment B" to the compartment B container labels, positioning it near the right topmost corner of compartment B for identification.

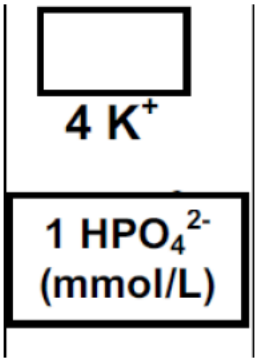
   This is the example Compartment A graphic from your PrismaSol products:

   [redacted] (b) (4)

3. We recommend capitalizing the first letter "P" in the name Phoxillum BK 4/2.5 and Phoxillum B22K4/0 to improve readability of the proprietary names, and consider using the same font, type, size, and typography for the letter "x" to minimize the unintentional interpretation of "pho" and "illum" as separate words.

B. Carton Labeling

1. Relocate the "4 K^+" statement inside the box. As currently presented, it is inconsistent with presentation of other information such as "1 HPO_4^{2-}" on the carton labeling.



APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Phoxillum that Gambro Renal Products, Inc. submitted on July 23, 2014.

Table 2. Relevant Product Information for Phoxillum

Initial Approval Date	N/A
Active Ingredient	Calcium/ Magnesium/ Sodium/ Potassium / Sodium bicarbonate/ Dibasic sodium phosphate
Indication	Indicated in adults and children for use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolytes and acid-base imbalances. It may also be used in case of drug poisoning when CRRT is used to remove filterable substances.
Route of Administration	Administered into the extracorporeal circuit before (pre-dilution) and/or after the hemofilter or hemodiafilter (post-dilution).
Dosage Form	Solution
Strength	*After reconstitution of compartments A and B, 1000 mL of the reconstituted solution contains:*

Active Ingredients in mEq/L except where noted	Phoxillum BK4/2.5	Phoxillum B22K4/0
Calcium Ca^{2+}	2.5	0
Bicarbonate HCO_3^-	32	22
Potassium K^+	4.0	4.0
Magnesium Mg^{2+}	1.5	1.5
Sodium Na^+	140	140
Phosphate HPO_4^{2-}	1 mmol/L	1 mmol/L
Chloride Cl^-	114.5	122

Dose and Frequency	Mode of therapy, solute formulations, flow rates, and length of therapy should be selected by the physician responsible for managing treatment depending on the clinical condition of the patient as well as the patient's fluid, electrolyte, and acid-base balance.
How Supplied	Two compartment bag made of Polyvinyl chloride (PVC). 5000 mL bag is composed of a small compartment (250 mL) and a large compartment (4750 mL). Two compartments are separated by a red frangible pin. Bag is overwrapped with a transparent overwrap.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15º-30ºC (59º-86ºF).

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on September 29, 2014 using the criteria in Table 3. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**May 13, 2013 to September 29, 2014**
Product	PrismaSol B22GK2/0; Prismasol B22GK4/0; Prismasol BGK0/2.5; Prismasol BGK2/0; Prismasol BGK2/3.5; Prismasol BGK4/0/1.2; Prismasol BGK4/2.5; Prismasol BK0/0/1.2 [product name]
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

The date search was limited from May 13, 2013, which is the date of our last search in OSE RCM# 2013-1109 related to the PrismaSol product.

B.2 Results

Our search identified zero cases.

B.3 List of FAERS Case Numbers

N/A

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on September 29, 2014 using the terms, PrismaSol, to identify any label and labeling reviews previously performed by DMEPA that may be relevant to this current review of Gambro's current proposed product, Phoxillum B22K4/0 and Phoxillum BK4/2.5.

C.2 Results

Our search identified one previous relevant review[1], and it appears Gambro did not implement our previous recommendations for PrismaSol. For our previous recommendations for PrismaSol that are applicable to this review of Phoxillum B22K4/0 and Phoxillum BK4/2.5, we make these recommendations in Section 4.1 of this review.

[1] Defronzo, K. Label and Labeling Review for PrismaSol Solution (NDA 021703/S-010). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 May 28. 13 p. OSE RCM No.: 2013-1109.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Phoxillum B22K4/0 and Phoxillum BK4/2.5 labels and labeling submitted by Gambro on July 23, 2014.

- Container Label
- Carton Labeling
- Prescribing Information

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

GRACE JONES
10/09/2014

CHI-MING TU
10/09/2014

Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207026

Application Type: New NDA

Name of Drug/Dosage Form: Phoxilium Sterile Solutions

Applicant: Gambro Renal Products

Receipt Date: March 13, 2014

Goal Date: January 13, 2015

1. Regulatory History and Applicant's Main Proposals

On March 13, 2014, the applicant submitted their NDA for Phoxilium (BK4/2.5 and B22K4/0). Based on the comparative electrolyte concentrations to the already approved PrismaSol Solutions under NDA 21703, the applicant will cross reference the clinical and nonclinical portions of the NDA.

Orphan Designation granted February 14, 2014 (#1203820).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 30, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

Selected Requirements of Prescribing Information

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *There's no 1/2 inch margin on all sides*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- *No white space above DOSAGE AND ADMINISTRATION*
- *White space included after each major heading*
- *Initial U.S. Approval Date omitted*

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *No references are made to the sections or subsections of the FPI*

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Patient Counseling Information Statement missing*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

NO 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Omitted*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *Omitted*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Date needs to be updated*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

NO 25. The TOC should be in a two-column format.

Comment: *Single column format*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subheadings are bolded*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Patient Counseling omitted.*

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *None included*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

NO 38. If no Contraindications are known, this section must state "None."

Comment: *The applicant included the following:* (b) (4)

ADVERSE REACTIONS Section in the FPI

N/A 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

    Comment: *Not included*

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

    Comment:

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

/s/

ANNA J PARK
04/29/2014