

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207026Orig1s000

MEDICAL REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 207026 PHOXILLUM replacement solution for continuous renal replacement therapy (CRRT).

Sponsor: Gambro Lundia AB

Review date: 12 January 2015

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 207026

This memo conveys the Division's decision to approve this application.

This application has been the subject of reviews of CMC (McLamore-Hines; 12 November 2014), biopharmaceutics (Eriadiri; 29 April 2014), microbiology (Miller; 12 November 2014), clinical effectiveness and safety (Xiao; 19 December 2014).

There is also a CDTL memo (Sapru; 8 January 2014), with which I am in complete agreement. I comment here on a few novel aspects.

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.

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/s/

NORMAN L STOCKBRIDGE
01/12/2015

Clinical Memo for Phoxillum NDA 207-026

Subject: Applicant's proposed revisions to the drug label (b) (4)
(b) (4) (email correspondence to Anna Park dated November 20, 2014)

Clinical Reviewer: Shen Xiao, MD, PhD

Clinical Team Leader: Aliza Thompson, MD

Background: On March 13, 2014, Gambro Lundia AB submitted a 505 (b)(2) application for Phoxillum solutions for use as a replacement solution in patients undergoing continuous renal replacement therapy (CRRT). Unlike PrismaSol, approved under NDA 21-703 for use as a replacement solution in patients undergoing CRRT, Phoxillum solutions contain phosphate. As agreed upon by the Division, the Phoxillum application references the clinical and non-clinical data contained in PrismaSol's NDA and hence the application that was submitted in March did not contain any clinical data.

On October 13, 2014, the applicant informed the Division that they had received three reports from one hospital in Great Britain related to metabolic acidosis (not resolving or worsening) in patients undergoing CRRT with Phoxillum. Phoxillum is currently marketed in Europe and has a slightly higher concentration of phosphate than what is proposed in the U.S. product (1.2 mmol/L of phosphate vs. 1.0 mmol/L). At the Division's request, the applicant submitted the narratives along with their analysis of these cases on November 20, 2014.

Based on these cases as well as information in the published literature, Gambro is proposing revisions to the drug label (b) (4)

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 (b) (4)

(u) (4)

(u) (4)

Reviewer's comment: I agree.

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

References:

1. Chua H, et al: Biochemical effects of phosphate containing replacement fluid for CVVH. Blood Purif 2012, 34: 306-312
2. Chua H, et al: Phoxilium vs Hemosol-B0 for continuous renal replacement therapy in acute kidney injury. Journal of critical care 2013, 28 (5); 884

Case reports and analyzes from Applicant:

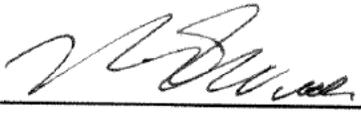
The following table presents three case reports received from a single hospital in the UK involving reports of acidosis in patients using Phoxilium. A brief narrative of each case report is provided, along with Baxter's pharmacovigilance assessment.

Case ID	Brief Narrative
2014BAX020514	<p>This is one of three spontaneous case reports that Baxter/Gambro received from one reporter in the UK (Glenfield Hospital, Leicester), each with the event of "worsening acidosis." Each patient had underlying metabolic acidosis and began CVVHDF treatment with Phoxilium (batch 740334). The hospital was apparently experiencing a calcium supply shortage and used heparin therapy rather than citrate therapy for anticoagulation of the extracorporeal circuit.</p> <p>This patient experienced worsening acidosis and rapid CO₂ increase and was acidotic and hyperphosphatemic before treatment with Phoxilium was initiated. The patient was not sedated since they were not invasively ventilated but he was on continuous positive airway pressure (CPAP). The patient commenced CVVHDF with Phoxilium with heparin anticoagulation. During treatment with Phoxilium the patient's phosphate level reduced to 1.8mg/dl but on 16April2014 the patient experienced a decline of pH that coincided with a rapid CO₂ increase. It was suspected that the patient may have been disorientated (due to neuroleptics) and could have removed his CPAP mask. He was switched to CVVHD without increasing dialysate flow in a possible attempt to improve acidosis and then back to CVVHDF with an increased dose of around 40 ml/kg/min. At around 1pm, Phoxilium was replaced by PrismaSol 4. His pH was low before and during treatment (7.2) and normalized during PrismaSol 4 therapy. His lactate was reported to be stable, as was his CO₂ (with the exception of the increase coinciding with pH decline).</p> <p>MEDICAL HISTORY: METABOLIC ACIDOSIS, CORONARY ARTERY DISEASE, PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY, CHRONIC KIDNEY DISEASE, DIABETES MELLITUS, HYPERPHOSPHATEMIA, ACIDOSIS CONCOMITANT THERAPY: Neuroleptics, standard ICU meds and PHOSPHATE SANDOZ.</p> <p>Baxter comment: <i>Due to the temporal relationship provided, the event of WORSENING ACIDOSIS is assessed as possibly associated with Phoxilium, though highly plausible alternative etiologies include the patient's respiratory status as well as his extensive past medical history. The event of RAPID CO₂ INCREASE appears to be related to the patient's respiratory status (disoriented and possibly removed his CPAP mask).</i></p>
2014BAX030650	<p>This is one of three spontaneous case reports that Baxter/Gambro received from one reporter in the UK (Glenfield Hospital, Leicester), each with the event of "worsening acidosis." Each patient had underlying metabolic acidosis and began CVVHDF treatment with Phoxilium (batch 740334). The hospital was apparently experiencing a calcium supply shortage and used heparin therapy rather than citrate therapy for anticoagulation of the extracorporeal circuit.</p> <p>A 43-year-old male patient became severely metabolically acidotic on CVVHDF using Phoxilium as pre & post replacement flows and dialysis flows. Due to a calcium supply shortage, citrate therapy was not running and the patient was on heparin circuit therapy. Despite high flow rates within prescribed range, acidosis worsened with nil improvement over many hours. When dialysis was turned off on one patient acidosis improved within 30-60 mins. The patient had no Lactate Acidosis. When Phoxilium bags swapped to PrismaSol 4 acidosis improved. This product was used off label for indication in this patient. The patient also had treatment interrupted several times.</p>

	<p>Baxter comment: Due to the temporal relationship provided, the event of WORSENING ACIDOSIS is assessed as possibly associated with Phoxilium. The limited amount of information provided limits a full medical assessment.</p>
2014BAX060010	<p>This is one of three spontaneous case reports that Baxter/Gambro received from one reporter in the UK (Glenfield Hospital, Leicester), each with the event of "worsening acidosis." Each patient had underlying metabolic acidosis and began CVVHDF treatment with Phoxilium (batch 740334). The hospital was apparently experiencing a calcium supply shortage and used heparin therapy rather than citrate therapy for anticoagulation of the extracorporeal circuit.</p> <p>A 43-year-old male patient became severely metabolically acidotic on CVVHDF using Phoxilium as pre & post replacement flows and dialysis flows (due to calcium supply shortage, citrate therapy not running, currently on heparin circuit therapy). Despite high flow rates within prescribed range, acidosis worsening with nil improvement over many hours. When dialysis was turned off on one patient acidosis improved within 30-60 mins. The patient had no Lactate Acidosis. When Phoxilium bags swapped to PrismaSol 4 acidosis improved. This product was used off label for indication in this patient. The patient also had treatment interrupted several times.</p> <p>On an unreported date the patient experienced a pneumothorax and had a chest drain inserted.</p> <p>Baxter comment: Due to the temporal relationship provided, the event of WORSENING ACIDOSIS is assessed as possibly associated with Phoxilium. The limited amount of information provided limits a full medical assessment, though a plausible alternative etiology includes the patient's respiratory status (pneumothorax with chest tube insertion). The event of PNEUMOTHORAX is more likely to be related to the patient's medical history or to a pulmonary etiology rather than to Phoxilium itself.</p>

Approval:

Signature:


 Medical Director, Global Pharmacovigilance
 M. Sherwood, MD

Date: 05 Nov 2014

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/s/

SHEN XIAO
12/19/2014

ALIZA M THOMPSON
12/19/2014