CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-703

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-703 (Prismasol)
Sponsor: Gambro Renal Products
Review date: 24 October 2006

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

Distribution: NDA 21-703

HFD-110/Paraoan
HFD-110/Xiao

Prismasol is a 9-member set of sterile solutions for use to replace water and to correct acid-base and electrolyte disturbances caused during Continuous Renal Replacement Therapy (CRRT; hemofiltration, hemodiafiltration, and hemodialysis). The various solutions contain sodium, potassium, calcium, magnesium, chloride, dextrose, lactate, and bicarbonate only, in different combinations and amounts. Thus there are no novel or foreign molecular species and what constituents there are are not what one would ordinarily mean by "drugs". Their actions are not receptor-mediated and they are not heir to the complex potential interactions of drugs.

The sponsor conducted no clinical trials, but there were published accounts of these or similarly constituted solutions as infusates for hemofiltration or hemodiafiltration. These publications were reviewed by medical officer Shen Xiao (7 July 2006). And they formed the basis for his recommendation that Prismasol be approved. In addition, the concentrations of constituents were selected to normalize electrolytes and acid-base. Their choices appear to be reasonable based on the effects of CRRT.

Other infusate constituents—e.g., phosphate—may need to be added, but individualization of treatment renders it impractical to manufacture solutions suitable for all possible clinical scenarios. Thus, labeling provides some basic advice, but the instructions for use heavily rely on the physician's judgment about how to perform CRRT.

Former Cardio-Renal Division Director Raymond Lipicky espoused a policy that all new dialysis solutions needed clinical outcome data to support their use and the contribution of individual components, even of they had no novel constituents, represented small differences from approved products, and had composition within the normal range. Hemodialysates (handled as devices by CDRH) have never been subject to these constraints. The CDER policy was largely overturned in a memo by then Division Director Doug Throckmorton (5 February 2004), which said we would consider new variants of an existing solution to be changes to dose and we would exercise some discretion in deciding to request clinical data to support proposed changes.

As with the recently approved Normocarb HF (NDA 21-910), in the current application, the publications would not have been sufficient had we felt there was a need for clinical data supporting effectiveness or safety. However, the current view is that infusates [redacted] are, effectively, bulk parenterals. The consequences of their use are predictable from first principles. Within a certain region of physiological and near-physiological concentrations, the effects can be predicted with sufficient accuracy that no clinical experience is indicated to confirm them. The concentrations of electrolytes in Prismasol are well within the bounds of comfort.

The reviews of microbiology (John Metcalfe; 19 May 2006) and chemistry (Sherita McLamore; 10 July 2006, 13 October 2006) recommend approval.

The NDA supports approval of 9 different formulations of Prismasol. Since the sponsor intends to market only 7, two are not mentioned in negotiated labeling.

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/s/

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