FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting
FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, MD
September 13, 2012

NDA 203826, phenylephrine hydrochloride injection **(Afternoon Session)**

DRAFT QUESTIONS

Intravenous (IV) phenylephrine has been marketed for several decades. In support of the proposed indication "to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension," the sponsor has submitted a publication-based application. A majority (42/50) of the clinical trials in adults were based on treatment or maintenance of blood pressure in peri-operative situations; eight publications involved patients with sepsis or septic shock.

1. **(DISCUSSION):** We are interested in the type of evidence needed to establish clinical benefit for this drug to be used for the treatment of acute hypotension. The type of evidence could range from an increase in BP to more stringent requirements, i.e., avoidance of irreversible morbidity or improvement in survival. Between these extremes, some might view improvements in organ function, organ and/or tissue perfusion, or tissue oxygenation as clinical benefits. We recognize that the type of evidence could depend on the specific clinical setting.

   Please discuss your views on the type of evidence needed to demonstrate a clinical benefit in the setting of:

   a. shock
   b. peri-operative hypotension
   c. "acute hypotensive states" in general

2. **(DISCUSSION):** The evidence of effectiveness for phenylephrine is derived from the published literature. Given the limitations of these studies and our inability to document their methodology and results, how much should the Agency rely on these studies?

3. **(DISCUSSION):** Safety data in the application were obtained from publications and postmarketing reports.

   There is no overall analysis of exposure.

   a. How confident are you that the safety profile has been adequately characterized in the submission?

   b. Is there additional safety information that the Agency should request? If so, should this information be requested pre-approval or post approval?

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DRAFT QUESTIONS (cont.)

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4. **(VOTE):** Should phenylephrine be approved "to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension?"

   a. **(DISCUSSION):** If not, is there a claim for which you think that phenylephrine should be approved, for example, "acute hypotensive states," or "hypotension associated with shock," or "peri-operative hypotension?" Other claims?

   b. **(DISCUSSION):** If you believe that phenylephrine should not be approved, what additional information is needed?