CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203826Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 203826 phenylephrine hydrochloride to increase blood pressure in "acute hypotensive states".

Sponsor: West-Ward Pharmaceuticals

Review date: 20 December 2012

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

Distribution: NDA 203826

This application was previously given a Complete Response (memo of 9 November 2012) with the only issue being negotiation of the timeframe for completing a PMR relating to a study in children. The sponsor has proposed a timeframe that is acceptable to DCaRP, DAAAP, and PeRC.

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I previously (memo of 19 October) concluded that this application was approvable. An initial consensus was reached to waive requirements under PREA, and agreement with PERC was obtained. Subsequently, DAAAP altered its opinion regarding the need for data in children age 12 and up, and since the responsibility for this application devolves to them upon approval, it seemed appropriate to honor their request for a PREA study. Time did not permit negotiation of the details or timing with the sponsor, so a Complete Response letter will now be issued, naming the PMR as the sole barrier to approval.

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This memo conveys the Division's recommendation to issue an Approval letter for phenylephrine hydrochloride.

This application has been the subject of reviews of CMC (Wilson-Lee, 5 September and 17 October 2012), biopharmaceutics (Chikhale, 8 March 2012), microbiology (Pfeiler, 21 March 2012), pharmacology/toxicology (Gatti, 30 May 2012), clinical pharmacology (Hariharan, 15 August 2012), medical (Targum, 11 August 2012), statistics (Liu, 10 August 2012). There is a comprehensive CDTL memo (Targum, 25 September 2012) with which I am largely in agreement.

Phenylephrine is an alpha-1 adrenergic receptor agonist, marketed since before any of the review team was born. The intravenous product has not previously been approved. This application was encouraged by CDER.

The support for effectiveness and safety is all derived from literature. No protocols nor data nor study reports were available, and no non-clinical nor clinical sites were inspected. However, the team and I are persuaded of the effectiveness and safety generally through the many publications and the generally consistent tale they tell.

Of note, the non-clinical data were not particularly informative, giving little insight into what vascular beds are acted upon, not giving the usual detailed view of off-target toxicology. There are published carcinogenicity studies, but irrelevant for the intended use. I have dropped (b) (4).

The dose-response and pharmacokinetic properties of phenylephrine are moderately well established, so that instructions for use, much as the literature supports, are defined.

Phenylephrine vasoconstricts in systemic and pulmonary vascular beds, but a finer description of effects by bed is not available in any setting of use.

Vasoconstriction raises blood pressure, which the team, the Advisory Committee, and I all agree represents a self-evident benefit in shock and shock-like settings threatening ischemic damage to organs.

The vasopressor effects are best characterized and generally better supported as clinically beneficial in settings of perioperative use, but it is also pretty clearly a pressor in other conditions with hypoperfusion attributable largely to extreme vasodilation, i.e., some, but not all, forms of shock. I have extended the claim into these settings, and the label provides some guidelines for dosing.

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/s/

NORMAN L STOCKBRIDGE
12/20/2012