

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204300Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## BRIEF STATISTICAL COMMUNICATION

**NDA / Suppl. No.** NDA 204300 / 0

**Drug Name:** Phenylephrine Hydrochloride injection, USP, 1%

**Indication(s):** Treatment [REDACTED] <sup>(b) (4)</sup> of hypotension during anesthesia

**Applicant:** Eclat Pharmaceuticals, Inc.

**Date(s):** Received 6/28/13; PDUFA Goal date 4/28/14

  

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Janice Derr, Ph.D.

**Concurring Reviewers:** Thomas Permutt, Ph.D.

  

**Medical Division:** Division of Anesthesia, Analgesia Products and Addiction Products

**Clinical Team:** Tim Jiang, M.D., Clinical Reviewer; Chris Breder, M.D., Clinical Team Leader

**Project Manager:** Kim Compton

  

**Keywords:** NDA Review

## 1. Purpose of this brief communication

The purpose of this brief communication is to describe a statistical review comment that I recommend including in Dr. Jiang's clinical review. The comment is shown in Exhibit 1. I am not providing a full statistical review of this submission, but I am providing statistical input as needed.

## 2. Background

Phenylephrine is a synthetic sympathomimetic amine. Its major action is on the cardiovascular system. Phenylephrine reverses anesthesia-induced hypotension by causing vasoconstriction, increasing systolic, diastolic and mean arterial pressure. Phenylephrine was patented in 1934 and has been used for a variety of indications. Although phenylephrine is a component of a variety of approved oral and intranasal medications for treatment of nasal congestion and topical formulations for local vasoconstriction, it has not received FDA approval as an injectable drug despite its use in the operating suite<sup>1</sup>.

The applicant submitted an NDA for Phenylephrine Hydrochloride injection, USP, 1%, on February 8, 2013. The applicant proposed to rely only on literature references for approval. The proposed claim was for the treatment [REDACTED]<sup>(b) (4)</sup> of hypotension during anesthesia. On April 5, 2013, the Agency issued a refuse-to-file letter for this application because the integrated summaries of efficacy and safety were not adequately constructed and did not contain separate discussions of each proposed indication.

The applicant met with the Agency of June 13, 2013 to discuss the revisions necessary to allow resubmission of the application and acceptance for filing. As requested by the Division, the resubmission included two separate ISEs, [REDACTED]<sup>(b) (4)</sup> one for the treatment claim.

## 3. Brief statistical review comment

Of the nineteen published studies that the applicant identified that support the use [REDACTED]<sup>(b) (4)</sup>, four publications described results from placebo-controlled studies. Dr. Jiang asked me to read these four publications, and to comment on his summary of the studies. In addition to providing minor edits to his summary, I proposed that he include the following paragraph in his review:

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<sup>1</sup> The source of this paragraph is the applicant's NDA submission, Part 2.5 (Clinical Overview).

**Exhibit 1. Statistical review comment recommended for inclusion in Dr. Jiang’s clinical review**

From a statistical perspective, we note that each reference reports p-values from a large number of statistical tests. The p-values come from several sources, including multiple endpoints, multiple points in time, and multiple pairwise comparisons in designs with more than two randomized study arms. The term “statistically significant” refers to the nominal alpha level of 0.05 applied to each p-value without adjustment for multiplicity. I believe that the results from the studies that are reported in these references provide reasonable support for the efficacy of phenylephrine for the proposed indication.

(b) (4)

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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.**  
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/s/  
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JANICE A DERR  
12/30/2013

THOMAS J PERMUTT  
12/30/2013  
I concur