CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203510Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	203-510
Submission Date(s):	September 21, 2012
PUDFA:	March 21, 2013
Drug	Phenylephrine hydrochloride
Product/Formulation; Strength(s)	Phenylephrine hydrochloride ophthalmic solution 2.5% and 10%
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip Colangelo, Pharm D, Ph D
OCP Division	DCP4
OND Division	DTOP/OAP
Applicant	Paragon Bioteck Inc.
Proposed indication	To dilate the pupil [redacted] (b) (4)
Dose and Administration	One drop should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye; If necessary, this dose may be repeated (b) (4) [redacted]
Submission Type	505(b)(2) ; Priority

BACKGROUND

Phenylephrine is an alpha-adrenergic receptor sympathetic agonist that has been used for more than 70 years to dilate the pupil in ocular diagnostic, therapeutic and surgical procedures. Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, are currently being marketed and supplied in the US for use as a mydriatic. However, these products are outside of the approved OTC monograph (i.e., between 0.08% and 0.2%) and have never been cleared by a FDA approval process. To address this unapproved drug product issue, the sponsor submitted this NDA as a 505(b)(2) application on 10/19/2011. The Refusal to File (RTF) letter was issued on 12/16/2011, citing CMC deficiencies. The sponsor resubmitted the NDA on 12/21/2012 and the application is now under the priority review.

Due to the wealth of scientific literature and extensive clinical use the sponsor considers that the safety and efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, have been well established. Therefore, the sponsor believes it is unnecessary to conduct any additional clinical studies to support this literature-based NDA.

The sponsor did not conduct any clinical pharmacology related studies and did not request the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(e) – "*FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health*", the Clinical Pharmacology review team will grant the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA, considering the extensive clinical experience of the product.

Reference ID: 3229562

RECOMMENDATIONS

The office of Clinical Pharmacology, Division of Clinical Pharmacology IV has reviewed the submission, and it is acceptable from a clinical pharmacology perspective. Product labeling should be revised as indicated in **Appendix 1**.

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Appendix 1. Proposed Labeling with Revisions

Sponsor's draft label version date: 11/2011

The following proposed labeling has been marked with revisions made by the Clinical Pharmacology Reviewer.

(underline =Clin Pharm reviewer's addition; ~~strikethrough~~ = Clin Pharm reviewer's deletion)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3229562

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/s/

YONGHENG ZHANG
12/12/2012

PHILIP M COLANGELO
12/12/2012

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	203-510
Drug Name:	Phenylephrine hydrochloride ophthalmic solution 2.5% and 10%
Applicant:	Paragon Bioteck Inc.
Submission Date:	September 21, 2012
Filing Date:	November 20, 2012
PDUFA Date:	July 21, 2013
OCP Primary Reviewer:	Yongheng Zhang, Ph D
OCP Team Leader:	Philip Colangelo, Pharm D, Ph D

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***YES***			*No clinical pharmacology studies were conducted and submitted. The requirement for submission of in vivo BA or BE data can be waived.*
Fileability Review Components				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	☐	☐	☒	*No clinical pharmacology studies were conducted and submitted*
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	☐	☐	☒	*As above*
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	☐	☐	☒	*No clinical studies were conducted and submitted*
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	☐	☐	☒	*No clinical pharmacology studies were conducted and submitted*
5. Are complete and relevant bioanalytical reports included in the NDA submission?	☐	☐	☒	*As above*
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☐	☒	☐	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☐	☐	☒	*No clinical pharmacology studies were conducted and submitted*

OCP Primary Reviewer _____ Date _____

OCP Team Leader _____ Date _____

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/s/

YONGHENG ZHANG
10/31/2012

PHILIP M COLANGELO
11/02/2012

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	203-510
Drug Name:	Phenylephrine hydrochloride ophthalmic solution 2.5% and 10%
Applicant:	Paragon Bioteck Inc.
Submission Date:	October 19, 2011
Filing Date:	December 20, 2011
PDUFA Date:	April 21, 2012
OCP Primary Reviewer:	Yongheng Zhang, Ph D
OCP Team Leader:	Philip Colangelo, Pharm D, Ph D

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***YES***			*No clinical pharmacology studies were conducted and submitted. The requirement for submission of in vivo BA or BE data can be waived.*
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5. Are complete and relevant bioanalytical reports included in the NDA submission?	☐	☐	☒	*As above*
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☐	☒	☐	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☐	☐	☒	*No clinical pharmacology studies were conducted and submitted*

OCP Primary Reviewer _____ Date _____

OCP Team Leader _____ Date _____

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/s/

YONGHENG ZHANG
12/01/2011

PHILIP M COLANGELO
12/01/2011