

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207926Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207926

SUPPL #

HFD #

Trade Name N/A

Generic Name Phenylephrine Hydrochloride Ophthalmic Solution

Applicant Name Akorn, Inc.

Approval Date, If Known January 15, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 203510

Paragon Biotech, Inc.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

This is a 505(b)(2) literature only NDA application

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|--|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| <i>*Only literature references, no clinical investigations conducted by applicant</i> | | |
| Investigation #2 | YES <input type="checkbox"/> | NO <input type="checkbox"/> |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|--|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| <i>*Only literature references, no clinical investigations conducted by applicant</i> | | |

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

No new investigations were submitted. This is a 505(b)(2) literature only application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ***No clinical investigations conducted by applicant*** !

IND # YES ! NO
! Explain:

Investigation #2 !

IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ***No clinical investigations conducted by applicant*** !

YES

Explain:

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Eithu Z. Lwin

Title: Regulatory Health Project Manager

Date: January 20, 2015

Name of Office/Division Director signing form: Renata Albrecht, MD

Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EI THU Z LWIN
01/20/2015
NDA 207926 exclusivity summary

RENATA ALBRECHT
01/21/2015

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--------------------------------------|--|
| NDA # 207926 BLA # | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: N/A Established/Proper Name: phenylephrine hydrochloride Dosage Form: ophthalmic solution, 2.5% and 10% | | Applicant: Akorn, Inc. Agent for Applicant (if applicable): |
| RPM: Eithu Z. Lwin | | Division: Division of Transplant and Ophthalmology Products |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) | | <p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 11/19/14</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 11, 2015</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> | | <input checked="" type="checkbox"/> None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | | <input type="checkbox"/> Received |
| ❖ Application Characteristics ³ | | |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 7
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Public communications (<i>approvals only</i>) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| • Indicate what types (if any) of information were issued | <input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| CONTENTS OF ACTION PACKAGE | |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

| Action Letters | |
|--|--|
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Approval 1/15/2015 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | <input checked="" type="checkbox"/> Applicant's 1/14/2015 |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included 7/11/2014 |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input type="checkbox"/> Included |
| ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> Most-recent draft labeling | <input checked="" type="checkbox"/> Applicant's 12/16/2014 |
| <ul style="list-style-type: none"> Original Labeling | <input checked="" type="checkbox"/> Included 7/11/2014 |
| ❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) | Applicant did not request proprietary name for this product |
| ❖ Labeling reviews (<i>indicate dates of reviews</i>) | RPM: <input checked="" type="checkbox"/> 12/11/2014 DMEPA: <input checked="" type="checkbox"/> 11/12/2014 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 12/5/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee ❖ 505(b)(2) Assessment Form | 9/9/2014 Cleared, email dated 12/22/2014 1/15/2015 |
| ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included 1/21/2015 |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|--|---|
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ | |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) | 1/12/2015, 12/11/2014, 12/5/2014, 12/3/2014, 11/21/2014, 10/28/2014, 9/4/2014, 8/29/2014, 8/27/2014, 8/25/2014, OGD-9/30/2013 |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | |
| ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | <input checked="" type="checkbox"/> N/A or no mtg Teleconference with the Sponsor on 4/3/2014, PIND 121700 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A |
| ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | 1/15/2015 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | 1/15/2015 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical | |
| ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review See CDTL review Review 1/9/2015 Filing Review 8/28/2014 <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | Page 18 of Clinical Review 1/9/2015 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |

| | |
|---|---|
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> N/A |
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input checked="" type="checkbox"/> None |
| ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> Cosigned primary review |
| Statistical Review(s) (<i>indicate date for each review</i>) | Review 10/30/2014 Filing Review 8/20/2014 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> Cosigned primary review |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | Review 12/8/2014 & 11/07/2014 Filing Review 8/19/2014 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) | <input checked="" type="checkbox"/> None requested |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> Cosigned primary review |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | Review 12/08/2014 Filing Review 8/6/2014 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None |
| ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) | <input checked="" type="checkbox"/> None requested |

| Product Quality <input type="checkbox"/> None | |
|---|--|
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> Cosigned primary review |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | Review 12/22/2014 Filing Review 9/3/2014 Biopharmaceutics Review 12/9/2014 |
| ❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | Review 12/22/2014 Filing Review 8/20/2014 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | Page 83 of CMC review 12/22/2014 |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | |
| ❖ Facilities Review/Inspection | |
| <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i> | Date completed: 8/14/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable OMPQ Filing Review 10/2/2014 |
| <input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i> | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review) |

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

| Day of Approval Activities | |
|--|---|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input checked="" type="checkbox"/> Done |
| ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>) |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input checked="" type="checkbox"/> Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | <input type="checkbox"/> Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name | <input type="checkbox"/> Done |
| ❖ Ensure Pediatric Record is accurate | <input type="checkbox"/> Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | <input checked="" type="checkbox"/> Done |

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/s/

EI THU Z LWIN
01/22/2015
NDA 207926

Lwin, Ei Thu

From: Holovac, Mary Ann
Sent: Monday, December 22, 2014 9:25 AM
To: Lwin, Ei Thu
Cc: Roeder, David L; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann
Subject: NDA 207926 Phenylephrine - cleared for action
Attachments: 505(b)(2) Assessment NDA 207926 12-11.doc; NDA 207926 patent-certification.pdf; NDA 207926 form-fda-356h-dated-12-11-2014.pdf

Eithu,

We discussed this application at the 12/8/14 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

No further changes are needed on the draft assessment you sent to me on 12/17/14 before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue.

Please let me know if you have any questions.

Mary Ann

From: Lwin, Ei Thu
Sent: Wednesday, December 17, 2014 9:11 AM
To: Holovac, Mary Ann
Cc: Roeder, David L; Bertha, Amy; Duvall, Beth A
Subject: RE: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510 - additional information needed

Good Morning CAPT Holovac,

Please review the attached amended 505(b)(2) Assessment, patent certification, and 356h for NDA 207926 phenylephrine. Please let me know if the committee requires any further revision or information.

Thank you,
Eithu

From: Holovac, Mary Ann
Sent: Tuesday, December 09, 2014 3:13 PM
To: Lwin, Ei Thu
Cc: Roeder, David L; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann
Subject: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510 - additional information needed

Hello Eithu,

The 505(b)(2) committee discussed this application again at yesterday's meeting and it was determined that the applicant should be asked to amend their patent certification as they submitted a paragraph II certification for a drug that they are not

relying upon. Modeling labeling on the approved Paragon does not constitute 505(b)(2) reliance. They should also submit a 356h that does not indicate reliance on Paragon Biotech NDA 203510 as NDA 207926 (Akorn) is literature based only.

Additionally, in response to question 3 on the updated assessment, please remove references to the Paragon Biotech NDA so that the language reads as follows:

The proposed product relies entirely on literature.

(b) (4) The applicant has marketed the product without an approved application for many years. Most of the literature studies do not identify the source of the phenylephrine ophthalmic solution used in the study and some of the literature studies may have used the applicant's product. The proposed product is comparable with reports across a wide range of literature with regard to adverse reactions and effectiveness. The Division considers the data in the literature submitted in this NDA to be an adequate bridge.

Please let me know if you have any questions and advise me of the applicant's response. Upon review of the amended patent certification, I anticipate clearing the application.

Thank you.

Mary Ann

From: Lwin, Ei Thu
Sent: Monday, December 08, 2014 11:00 AM
To: Holovac, Mary Ann
Subject: FW: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

Dear CAPT Holovac,

Please review the revised 505(b)(2) assessment for NDA 207926 phenylephrine. Please let me know if the revisions are acceptable or if I would need to change something. When is the next 505(b)(2) meeting for NDA 207926?

Thanks,
Eithu

From: Chambers, Wiley A
Sent: Thursday, December 04, 2014 9:16 AM
To: Holovac, Mary Ann
Cc: Roeder, David L; Boyd, William M; Lwin, Ei Thu
Subject: RE: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

Akorn claims to rely on the Paragon application because they follow the same format that Paragon used in their labeling. Akorn does not rely on any data generated by Paragon. There is no way that they could because Paragon did not perform any clinical or non-clinical studies themselves. Paragon obtained their clinical and non-clinical data entirely on literature. Akorn starts with the same literature as Paragon did and adds a couple of studies in which the Akorn product is specifically identified. Paragon did not include the studies in which the Akorn product was specifically identified.

Since the clinical and non-clinical data is essentially the same for each application (and none of the data was generated by either company), we will request that the package inserts look the same based on the data from the literature. We are not relying on the Paragon application for any data in our review of the Akorn application, but instead we are creating the same data the same way.

Wiley

From: Holovac, Mary Ann
Sent: Thursday, December 04, 2014 8:33 AM
To: Chambers, Wiley A
Subject: RE: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

Hello Dr. Chambers,

Thank you for the follow up information.

So to be perfectly clear, can the division confirm that there is no reliance then on **any portion** of Paragon Biotech's NDA?

This will need to be crystal clear in all administrative records if that is indeed the case...and if that is the case, Akorn will not be required to certify to the newly listed Paragon patent.

The 505(b)(2) assessment at a minimum will need to be revised as multiple sections of the Paragon labeling are noted as being relied upon in that document.

Thank you.
Mary Ann

From: Chambers, Wiley A
Sent: Thursday, December 04, 2014 7:40 AM
To: Holovac, Mary Ann
Subject: FW: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

From: Boyd, William M
Sent: Thursday, December 04, 2014 7:28 AM
To: Lwin, Ei Thu; Chambers, Wiley A; Rivera, Maria; Kotch, Lori E; Chelliah, Mariappan; Shanmugam, Balajee; Wang, Yan (CDER/DB4); Chefo, Solomon; Zhang, Yongheng; Colangelo, Philip M; Sweeney, Neal J; Zolnik, Banu S; Corser, Christine; Kapoor, Rachna
Cc: Milstein, Judit; Albrecht, Renata
Subject: RE: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

All portions of the application for which Akorn does not have right to reference come from literature sources for studies not conducted by/for Paragon.

Bill

From: Lwin, Ei Thu
Sent: Wednesday, November 26, 2014 2:11 PM
To: Boyd, William M; Chambers, Wiley A; Rivera, Maria; Kotch, Lori E; Chelliah, Mariappan; Shanmugam, Balajee; Wang, Yan (CDER/DB4); Chefo, Solomon; Zhang, Yongheng; Colangelo, Philip M; Sweeney, Neal J; Zolnik, Banu

S; Corser, Christine; Kapoor, Rachna
Cc: Milstein, Judit; Albrecht, Renata
Subject: FW: NDA 207926 Phenylephrine - reliance on Paragon Biotech's NDA 203510

Dear All,

This NDA got a bit more complex as there is a newly issued patent 8,859,623 that was listed in the Orange Book on Paragon Biotech's NDA 203510 in October 2014. Akorn's patent certification was provided to the agency prior to this patent was listed in the Orange Book.

The 505(b)(2) committee would like to know if there is any portion on this application's reliance NDA 203510 that could not be obtained from literature only sources. Currently Akorn's proposed package insert states the application is relying on Paragon Biotech's NDA 203510 for Dosage Administration, Contraindications, Warning and Precautions, Adverse Reactions, Drug Interactions, Use in Special Populations, Overdosage, and Clinical Pharmacology. It also states reliance on published literature for the same sections of the labeling (not inclusive of the drug interactions section).

Correspondence from 505(b)(2) committee is included below for further information.

Thank you,
Eithu

From: Holovac, Mary Ann
Sent: Wednesday, November 26, 2014 1:48 PM
To: Lwin, Ei Thu
Cc: Holovac, Mary Ann
Subject: RE: NDA 207926 Phenylephrine -

Hello Eithu,

We discussed the subject application at this past Monday's 505(b)(2) clearance committee meeting. The committee needs additional information as follow up to our Monday meeting. Can you assist?

The assessment states the application is relying on Paragon Biotech's NDA 203510 for Dosage Administration, Contraindications, Warning and Precautions, Adverse Reactions, Drug Interactions, Use in Special Populations, Overdosage, and Clinical Pharmacology. The assessment also states reliance on published literature for the same sections of the labeling (not inclusive of the drug interactions section).

The sponsor also indicates reliance on NDA 203510 and they provided a patent certification. This made total sense when the application was originally submitted under 505(j) but we need to confirm this reliance as it is now filed under 505(b)(2).

As a first step, the committee would like clarity/confirmation on this application's reliance NDA 203510 particularly with respect to any portion that could not be obtained from literature only sources.

Secondarily, once it is confirmed that this application definitively relies on some aspect of NDA 203510 – that could not be obtained from literature sources only – the agency will need to ask the applicant to address the newly issued patent 8,859,623 that was listed in the Orange Book on NDA 203510 in October 2014. Akorn's patent certification was provided to the agency prior to when this patent was listed in the Orange Book. We can address this/discuss further once we have an answer to the first question.

Thank you in advance and please do not hesitate to contact me if this is not clear.
Happy Thanksgiving.

Mary Ann

From: Lwin, Ei Thu
Sent: Friday, November 07, 2014 9:53 AM
To: Holovac, Mary Ann
Subject: RE: NDA 207926 Phenylephrine - Please schedule for 505(b)(2) assessment

Yes, the planned action is approval.

From: Holovac, Mary Ann
Sent: Friday, November 07, 2014 9:53 AM
To: Lwin, Ei Thu
Subject: RE: NDA 207926 Phenylephrine - Please schedule for 505(b)(2) assessment

Great, Thank you Eithu. May I assume the planned action is APPROVAL?
Mary Ann

From: Lwin, Ei Thu
Sent: Friday, November 07, 2014 9:33 AM
To: Holovac, Mary Ann
Subject: RE: NDA 207926 Phenylephrine - Please schedule for 505(b)(2) assessment

Good Morning CAPT Holovac,

Please see the attached 505(b)(2) Assessment and supporting documents for NDA 207926 phenylephrine by Akorn. Please let me know if there is anything else you need.

Thank you,
Eithu

Eithu Z. Lwin. PharmD, NCPS, CDE
LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

From: Holovac, Mary Ann
Sent: Friday, September 12, 2014 8:27 AM
To: Lwin, Ei Thu
Subject: RE: NDA 207926 Phenylephrine - Please schedule for 505(b)(2) assessment

Good morning Eithu,
I have adjusted the goal date in our tracking system. We don't schedule into our clearance meetings until the 505(b)(2) assessment has been received. You will need to send me this approximately 60 days in advance of when the division wants to take action. Please send me this document around 11/11/14 and I will work it into our clearance procedures.
Thank you.

Mary Ann

From: Lwin, Ei Thu
Sent: Friday, September 12, 2014 8:21 AM
To: Holovac, Mary Ann
Subject: NDA 207926 Phenylephrine - Please schedule for 505(b)(2) assessment
Importance: High

Good Morning Mary Ann,

NDA 207926 phenylephrine by Akorn is a 505(b)(2) application. During our filing/planning meeting on August 26, 2014, DSS has requested DTOP to expedite NDA 207926 phenylephrine Ophthalmic Solution by Akorn due to drug shortage. Although this application is classified as "standard" review (PDUFA date May, 11, 2015), we will be expediting the review of this application to complete in 6 months, and our internal goal date would be **January 11, 2015**. Please schedule us in the calendar for 505(b)(2) assessment.

Application: NDA 207926
Sponsor Akorn, Inc.
Drug Phenylephrine Hydrochloride ophthalmic solution 2.5% & 10%
Indication For dilation of the pupil
Received: July 11, 2014

Please let me know if you have any questions.

Thank you,

Eithu Z. Lwin, PharmD, NCPS, CDE
LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/15/2015

NDA 207926 phenylephrine 505(b)(2) Clearance

From: Lwin, Ei Thu

Sent: Monday, August 25, 2014 11:19 AM

To: Sam.boddapati@akorn.com

Subject: Your NDA 207926 phenylephrine - need revised 356h and please submit form 3542a

Dear Dr. Boddapati,

Upon review of your NDA 207926 I was unable to locate FDA Form 3542a. If there are no relevant patients, please complete section 5 and 6 of this form. Furthermore, in the FDA form 356h section 20, it states "see attached sheet." Please write in the name and NDA # for the Paragon Bio Teck's phenylephrine product. You cannot list ANDA product as the reference listed drug. Please resubmit those 2 forms to the NDA and let me know if you have any questions.

Thank you,

Eithu Z. Lwin, PharmD, CDE

LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6345

Silver Spring, MD 20993

Phone: 301-796-0728

Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/12/2015

NDA 207926 outgoing communication 8/25/2014

From: Lwin, Ei Thu
Sent: Tuesday, October 28, 2014 3:03 PM
To: Sam.boddapati@akorn.com
Subject: Your NDA 207926 Phenylephrine - need samples of the bottles

Dear Dr. Boddapati,

In order to complete labeling review for your NDA 207926, please send me samples of the bottles.

I will need a bottle sample for:

- a. Phenylephrine hydrochloride ophthalmic solution USP, 2.5%, 2ml fill size
- b. Phenylephrine hydrochloride ophthalmic solution USP, 2.5%, 15ml fill size
- c. Phenylephrine hydrochloride ophthalmic solution USP, 10%, 5ml fill size

Please send these samples to me at:

Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993

Please let me know if you have any questions regarding this email.

Thank you,

Eithu Z. Lwin, PharmD, NCPS, CDE

LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/12/2015

NDA 207926 outgoing communication 10/28/2014

From: Lwin, Ei Thu
Sent: Wednesday, December 03, 2014 9:38 AM
To: Sam.boddapati@akorn.com
Subject: NDA 207926 phenylephrine - 120 day safety update

Good Morning Sam,

As a gentle reminder, please submit the 120 day safety update for NDA 207926.

Thank you,

Eithu Z. Lwin, PharmD, NCPS, CDE

LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/12/2015

NDA 207926 outgoing communication 12/3/2014

From: Lwin, Ei Thu
Sent: Thursday, September 04, 2014 12:23 PM
To: 'Sam Boddapati'
Subject: RE: NDA 207926 -- phenylephrine trade name

Thank you, Sam, for the email.

From: Sam Boddapati [<mailto:sam.boddapati@akorn.com>]
Sent: Thursday, September 04, 2014 11:46 AM
To: Lwin, Ei Thu
Subject: NDA 207926 -- phenylephrine trade name

Hi Eithu

As mentioned in our phone conversation, I am confirming herewith that there is no Trade Name for Phenylephrine Hydrochloride Ophthalmic Solution. Akorn will market this with generic name as 'Phenylephrine Hydrochloride Ophthalmic Solution USP'

Let me know if you need any further clarification.

Thanks
Sam

Sam Boddapati, Ph.D.
Sr. Vice President, Regulatory Affairs
Akorn, Inc
Phone: 847-353-4909

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/s/

EI THU Z LWIN

01/12/2015

NDA 207926 outgoing communication 12/4/2014

From: Lwin, Ei Thu
Sent: Thursday, December 11, 2014 9:48 AM
To: Sam.boddapati@akorn.com
Subject: NDA 207926 phenylephrine labeling and resubmit new patent certification 356h
Importance: High

Good Morning Sam,

I have attached the revised labeling for phenylephrine NDA 207926 for your team to review for concurrence. I would appreciate if your team could work on it and get it back to us before the holiday.

On a different note, there is a new patent for Paragon Biotech phenylephrine NDA 203510 that was not present when Akorn initially submitted application for NDA 207926. In your initial submission you claim reliance on Paragon application. If Akorn application is literature based only, we would need you to amend your patent certification and resubmit 356h that does not indicate reliance on Paragon Biotech NDA 203510.

Please let me know if you have any questions.

Thank you,

Eithu Z. Lwin, PharmD, NCPS, CDE

LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/12/2015

NDA 207926 outgoing communication 12/11/2014

From: Lwin, Ei Thu
To: Sam.boddapati@akorn.com
Subject: NDA 207926 phenylephrine - revised PI - please submit by COB 1/16/15
Date: Monday, January 12, 2015 4:02:00 PM
Attachments: [Akorn phenylepherine PI - REVISED 1.12.15 Track Changes.docx](#)
[Akorn phenylepherine PI - REVISED 1.12.15 CLEAN.pdf](#)
Importance: High

Dear Dr. Boddapati,

I have attached revised PI for NDA 207926 phenylephrine for your team to review. One of the attachment is a Word Version with track changes and the other is PDF clean version. Please submit revised PI to the NDA as early as possible by the end of the week.

Please let me know if you have any questions.

Thank you,

Eithu Z. Lwin, PharmD, NCPS, CDE

LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

01/12/2015

N207926 outgoing communication 1.12.15

From: Bhandari, Navi
To: sam.boddapati@akorn.com
Subject: NDA 207926 Information Request
Date: Friday, December 05, 2014 7:00:00 AM
Attachments: [NDA 207926 IR3.pdf](#)
Importance: High

Good Morning Sam,

Please see the attached Information Request. Please confirm receipt.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815



NDA 207926

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, Ph.D., Sr. Vice President, Regulatory Affairs
1925 West Field Court
Suite 300
Lake Forest, IL 60045

Dear Dr. Boddapati:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride Ophthalmic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by November 11, 2014 in order to continue our evaluation of your NDA.

A. Please revise the drug product specification as given below

- 1) The proposed acceptance range for the phenylephrine hydrochloride assay in the stability specification is (b) (4)%. There is no overage in your drug product and the upper limit is not justified. Please revise the range to (b) (4)%.
- 2) Per ICH Q1R(2) guidelines, a (b) (4) is considered a significant change, specifically when the drug product is packaged in a (b) (4) container and stored at room temperature. The NMT (b) (4)% acceptance criteria you have proposed for the (b) (4) far exceeds this limit and is not supported by available (b) (4) data. Please tighten the specification for (b) (4) to NMT (b) (4)%.
- 3) We acknowledge your communication dated 25-Nov-2014 revising the limits for total degradants in the drug product release specification to NMT (b) (4)%. However, the acceptance criterion for total degradants over stability was not revised and remains at NMT (b) (4)% currently. Please note that the regulatory specification applies through end of shelf-life. Please also revise the total degradants in the stability specification to NMT (b) (4)%.
- 4) Include in the drug product specification (both over release and stability) a test for unidentified impurity with an acceptance limit of NMT (b) (4)%.

B. Please update the drug product specification in P.5.1 with the revised specification table showing the tests, test methods and acceptance criteria that apply through product release and shelf-life. Confirm that all the post-approval stability studies will be carried out as per the revised stability specification. Please note that the regulatory specifications apply over the product shelf-life.

- C. Although several documents titled, “Photostability Testing of Bulk Drug Substances and Drug Products”, are listed in the SOP index, we could not locate the reports in the NDA. Please provide these reports with data from the photostability studies or indicate where in the NDA they are provided.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rapti D.
Madurawe -A

Digitally signed by Rapti D. Madurawe -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300220251,
cn=Rapti D. Madurawe -A
Date: 2014.12.04 15:12:05 -05'00'



NDA 207926

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, Ph.D., Sr. Vice President, Regulatory Affairs
1925 West Field Court
Suite 300
Lake Forest, IL 60045

Dear Dr. Boddapati:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride Ophthalmic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by November 28, 2014 in order to continue our evaluation of your NDA.

1. The release specification for the drug product limits the total degradants at NMT ^(b)(4)%. Although the total degradant levels for the exhibit batches have not been measured, based on the available stability data we recommend that the total degradants be controlled at NMT ^(b)(4)%. Please revise and submit the updated specification table.
2. Please refer to the validation report titled, "Validation of Benzalkonium Chloride (BAC) in Phenylephrine HCl (AK-Dilate)" from ^(b)(4). Page 16 of this validation report references the Product Development Report for ^(b)(4) for the linearity requirements of BAC assay by Method III, RD045. We could not locate the above referenced report in the current NDA submission. Please indicate where in the NDA this report is located or provide the linearity, LOD and LOQ for the BAC assay method RD045.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Balajee
Shanmugam
-S

Digitally signed by Balajee
Shanmugam -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13002
17143, cn=Balajee Shanmugam -S
Date: 2014.11.21 11:27:03 -05'00'

From: Bhandari, Navi
To: "[Sam Boddapati](#)"
Bcc: [Shanmugam, Balajee](#)
Subject: Information Request NDA 207926- Quick Turnaround Requested
Date: Friday, November 21, 2014 12:18:00 PM
Attachments: [NDA 207926 IR2.pdf](#)
Importance: High

Good afternoon Sam,

Please see the attached information request and provide confirmation of receipt.

Please provide a response no later than November 28, 2014.

Thank you,
Navi



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: August 26, 2014

| | |
|--|--|
| To: Sam Boddapati, PhD Senior Vice President, Regulatory | From: Eithu Z. Lwin Regulatory Project Manager |
| Company: Akorn, Inc. | Division of Transplant and Ophthalmology Products |
| E-mail: sam.boddapati@akorn.com | E-mail: Eithu.Lwin@fda.hhs.gov |
| Phone Number: 847-353-4909 | Phone Number: 301-796-0728 |

Subject: Find enclosed comments on the initial submission for NDA 207926

Total no. of pages including cover: 2

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD, CDE
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 207926
Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%.
Applicant: Akorn, Inc.
Attention: Sam Boddapati, PhD

Dear Dr. Boddapati,
In order to continue with the timely review of your NDA, we request that you provide the following information by COB September 12, 2014.

Product Quality Microbiology

The application indicates that the drug product container/closure components are (b) (4) and that received container/closure components are accompanied by a (b) (4) Processing. Please provide container/closure sterilization process validation reports for these components. Alternatively you may reference a Drug Master File containing this information, and provide the corresponding Letter of Authorization citing the DMF submission date of the aforementioned validation data.

Please, let me know if you have any questions regarding this request.

Thank you,

Eithu Z. Lwin, PharmD, CDE
LT, U.S. Public Health Service
Regulatory Health Project Manager
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6345
Silver Spring, MD 20993
Phone: 301-796-0728
Fax: 301-796-9881

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/s/

EI THU Z LWIN

08/29/2014

NDA 207926 Micro Information Request



NDA 207926

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, Ph.D., Sr. Vice President, Regulatory Affairs
1925 West Field Court
Suite 300
Lake Forest, IL 60045

Dear Mr. Boddapati:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride Ophthalmic Solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by September 8, 2014 in order to continue our evaluation of your NDA.

1. The tables providing drug product specification in Section 3.2.P.5.1 includes information on (b)(4) in-process controls. This information should be provided in the appropriate sections of the NDA and not in the drug product specification. Drug product specification, per ICHQ6 includes a list of tests, references to analytical procedures and appropriate acceptance criteria. Submit the revised drug product specification and clearly distinguish the release and stability specification. Note that the regulatory specification apply through the shelf-life of the product.
2. The drug product specification does not specify the analytical method used for the identification test. Please update the drug product specification to include either one specific identity method or two non-specific tests (please see ICH Q6A). For example, two chromatographic procedures, where separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/ (b)(4), are generally acceptable.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM

08/27/2014

Signing for Dr. Rapti Madurawe



NDA 207926

NDA ACKNOWLEDGMENT

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory
1925 West Field Court, Suite 300
Lake Forest, IL 60045

Dear Dr. Boddapati:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

Date of Application: July 11, 2014

Date of Receipt: July 11, 2014

Our Reference Number: NDA 207926

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 9, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0728.

Sincerely,

{See appended electronic signature page}

Eithu Z. Lwin, PharmD, CDE
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

EI THU Z LWIN
07/25/2014
NDA 207926 ACK letter



PIND 121700

MEETING MINUTES

Akorn, Inc.
Attention: Sam Boddapati, Ph.D.
Senior Vice President, Regulatory Affairs
1925 West Field Court
Suite 300
Lake Forest, IL 60045

Dear Dr. Boddapati:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%.

We also refer to the Type-B teleconference held between representatives of your firm and the FDA on April 3, 2014.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time: April 3, 2014, 2:00 pm
Meeting Location: Teleconference
Meeting Type: Type B – Pre-IND
Application: PIND 121700
Drug: Phenylephrine HCL Ophthalmic Solution USP, 2.5% and 10%
Sponsor: Akorn, Inc.
Indication: For pupil dilation
Meeting Chair: Wiley Chambers
Meeting Recorder: Michael Puglisi

FDA PARTICIPANTS:

Renata Albrecht/ Division Director
Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Rhea Lloyd/ Medical Officer
Martin Nevitt/ Medical Officer
Maria Rivera/ Nonclinical Reviewer
David Roeder/ Associate Director, Regulatory Affairs, Office of Antimicrobial Products
Balajee Shanmugam/ Product Quality Team Leader
Abel Eshete/ Statistics Reviewer
Yan Wang/ Statistics Team Leader
Yongheng Zhang/ Clinical Pharmacology Reviewer
Philip Colangelo/ Clinical Pharmacology Team Leader
Michael Puglisi/ Regulatory Project Manager

SPONSOR PARTICIPANTS:

Sam Boddapati/ Senior Vice President, Regulatory Affairs
Biswajit Pati/ Vice President, Research and Development
Bharathi Devarakondo/ Manager, Regulatory Affairs
Mukul A. Agrawal/ Senior Pharmaceutical Sciences Consultant

MEETING OBJECTIVE:

To discuss the Agency's requirements for supporting data for a planned 505(b)(2) NDA application for Phenylephrine HCL Ophthalmic Solution USP, 2.5% and 10%, for pupil dilation.

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the February 28, 2014, background package (see bolded text below) were provided to the Sponsor in an email dated March 31, 2014, (see text in italics below). This meeting served to clarify those responses. The discussion during the meeting is reflected in normal font.

QUESTIONS FOR DISCUSSION:

REGULATORY/CLINICAL

- 1. Does the FDA concur that Akorn can file its New Drug Application (NDA) for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, under section 505(b)(2) based on the clinical and nonclinical literature data presented in the briefing document?**

Agency Response: Yes, as long as data is provided from at least two adequate and well-controlled trials using a product that can be linked (bridged) to your product for the indication being sought. Trials from published literature may be used.

Meeting Discussion: The Sponsor agreed they will provide at least two adequate and well controlled trials from published literature on Phenylephrine for the proposed indication. They stated that they have found five literature articles on studies of various procedures that included the use of their product, AK-Dilate for the dilation of the pupil. The Sponsor requested the Agency's guidance concerning data required for bridging of AK-Dilate to the data for the other products use in the published literature. The Agency stated that it will ultimately need to determine if the Sponsor's product is likely to perform in the same way as the products used in the published literature. Demonstrating that different formulations all perform the same way regardless of the additional ingredients they contain would be helpful if true. Post-marketing information from the history of use of the Sponsor's product could also be helpful. Published adequate and well controlled studies that used AK-Dilate would be the most helpful.

- 2. Akorn plans to use the labeling for the approved product (NDA 203510) as the basis for updating the labeling for its proposed ophthalmic solution product. Does the Agency find this approach acceptable?**

Agency Response: No. If you plan on referencing the Agency's previous findings of safety and efficacy for another product, you must provide a link (bridge) to that product.

Meeting Discussion: The Agency stated the Sponsor will have to bridge for the safety data in the same fashion as for the efficacy data. The Sponsor was discouraged from bridging to a product with a formulation that is known to be different.

- 3. Does the FDA concur with Akorn that the listed clinical efficacy studies in Tables 4 (clinical efficacy data) and 5 (AK-Dilate clinical data) and pharmacokinetic studies**

in Table 6 presented in the briefing document are sufficient to support the safety and efficacy of Akorn's phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, for the proposed indication?

Agency Response: *The question cannot be answered at this time. A determination of the adequacy of the data can only be made after review of the application.*

From a Clinical Pharmacology perspective, we agree that the pharmacokinetic (PK) studies provided in Table 6 of the briefing document are sufficient to support the submission of a 505(b)(2) NDA.

Meeting Discussion: The Agency stated it has no preference for a particular format for presenting the data in the NDA.

4.



Meeting Discussion: The Sponsor stated they will support the safety and efficacy in pediatric patients from the literature data presented in the NDA on Phenylephrine.

5. Does the FDA agree that sufficient information is available from the literature to support the filing of Akorn's NDA and that no further pre-clinical or clinical studies are necessary for the approval of Akorn's formulation?

Agency Response: *The question cannot be answered at this time. A filing determination can only be made after review of the application.*

Meeting Comment: There was no discussion of this matter during the teleconference.

6. As per 21 CFR 320.22 (b), Akorn intends to submit a waiver of the requirement to submit evidence of in vivo bioavailability or bioequivalence (BA/BE) for its phenylephrine hydrochloride ophthalmic solution 2.5% and 10% product with the NDA application. Does the Agency agree that phenylephrine hydrochloride ophthalmic solution is eligible for a BA/BE waiver?

Agency Response: *Agree.*

Meeting Comment: There was no discussion of this matter during the teleconference.

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

7. **Akorn plans to rely on the labeling for the approved reference product and the literature summarized in Tables 2 (preclinical data) and 3 (Ak-Dilate preclinical data) for the pre-clinical pharmacology and toxicology sections of its NDA. Does the FDA agree with this approach?**

Agency Response: We agree that the referenced information can be used to support submission of the NDA.

The NDA submission should include a summary of all published nonclinical literature being relied upon to support the NDA and a copy of all the publications cited. All required nonclinical elements should be provided, either directly (original studies or published literature) or by relying on the FDA's findings of safety and effectiveness for a listed drug or published literature and establishing an adequate bridge to the listed drug or published literature. See Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals for further information regarding required nonclinical elements.

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>)

Impurity specifications that exceed qualification limits specified in the ICHQ3 guidances should be adequately qualified and the supporting safety data should be provided in the NDA submission. Ensure that both ocular and systemic safety are addressed.

Meeting Comment: There was no discussion of this matter during the teleconference.

CHEMISTRY AND MANUFACTURING (CMC)

8. **Akorn plans to file the NDA with the CMC summary presented in the briefing document. Does the FDA agree that the CMC information is sufficient for the filing of NDA?**

Agency Response: The question cannot be answered at this time. The NDA should provide complete CMC information for the drug substance and drug product. The submission suggests that the drug substance will be referenced to a DMF. Please provide a LOA authorizing the Agency to reference the DMF. The NDA should identify all manufacturing and testing facilities, provide batch composition and formula for the two strengths, information on control of critical steps and intermediates, analytical method (including chiral method for [REDACTED] ^{(b) (4)} batch analyses, characterization of impurities, reference standards, information on container closure (and LOAs if referencing DMFs), stability (including stress test) and post-approval stability protocol and commitment. The NDA should also provide Executed batch records for the different strengths.

The drug product specification should follow ICH Q3 B guidelines in reporting impurities. A test for identity is proposed but there is no mention of the method. ICH Q6 recommends either one specific identity method or two non-specific tests.

Information on the following one-time tests should be submitted in the NDA:

- *Freeze-thaw cycling studies (3 cycles)*
- *Weight loss through expiry on primary stability batches*
- *Leachables/extractables on container/closure by using screening analytical methods (such as HPLC, GC etc.) and studies on at least one stability batch through expiry.*
- *Droplet volume evaluation from multiple container batches*

From a Product Quality Microbiology perspective, the information that you submitted in your briefing package is not sufficient for filing an NDA, as it only contains a summary of the manufacturing process as it pertains to product sterility. An NDA application should contain a full description of the manufacturing process, including process validation studies. For a full description of the microbiology information necessary for filing an NDA, see FDA's Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072171.pdf>).

Meeting Comment: The Sponsor mentioned that a (b)(4) method is currently being developed and asked if this test should be included in the specification. The Agency stated that it is likely the test will be part of the drug substance and drug product specification but the Sponsor can provide justification if they choose not to include it. Further, the Agency mentioned this is a review issue and a decision will be made upon review of the data.

- 9. Akorn accumulated stability data on Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% (2 mL and 15 mL Fill) and 10% (5 mL Fill) for number of lots (up to 24 months long-term and 3 months accelerated conditions). The available stability data on the listed lots will be provided in the NDA. Also, we have provided in the briefing document stability data on 3 pivotal lots for review. We have observed Individual Unknown Degradants with a limit of NMT (b)(4)% and Total Unknown Degradants NMT (b)(4)% during the shelf-life of the drug product. Does the FDA concur that this stability data is adequate for filing NDA?**

Agency Response: *We expect the NDA at the time of submission to include 12-months long-term and 6-months accelerated stability data for three registration batches. Per ICH Q1A (R2), two of the three batches at least should be of pilot scale. The stability samples should be tested for critical quality attributes under all storage conditions.*

Please refer to our response to Question 8 on reporting impurities. Acceptance of the proposed limits for any attribute is a review issue.

Meeting Discussion: There was no discussion of this matter during the teleconference.