

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**021951Orig1s000**

**OTHER REVIEW(S)**

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	CIP-ISOTRETINOIN (isotretinoin) capsules, for oral use
Applicant	Ranbaxy, Inc.
Application/Supplement Number	NDA 21951 S1
Type of Application	Original NDA
Indication(s)	Treatment of severe recalcitrant nodular acne in patients 12 years of age and older who are unresponsive to conventional therapy, including systemic antibiotics
Established Pharmacologic Class <sup>1</sup>	retinoid
Office/Division	ODEIII/DDDP
Division Project Manager	Matthew White
Receipt Date	November 29, 2011
PDUFA Goal Date	May 29, 2012
SEALD Review Date	May 21, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

# Selected Requirements of Prescribing Information (SRPI)

## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** *The DDDP will likely grant a waiver for the 1/2 page HL requirement.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *Add one line of white space between the Highlights limitation statement and the product title.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI

## Selected Requirements of Prescribing Information (SRPI)

• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

**YES**

12. All text must be **bolded**.

**Comment:**

**YES**

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

## Selected Requirements of Prescribing Information (SRPI)

**Comment:** *The Boxed Warning should be one box; not two boxes. Merge the two boxes into one box.*

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

**Comment:**

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

**Comment:**

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

**Comment:**

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

**Comment:**

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:**

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Include the revision date (e.g., May 2012).*

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

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## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

**Comment:** *The cross-references in the Boxed Warning in the FPI are incorrect.*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- YES** 42. All text is **bolded**.

**Comment:**

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information (SRPI)

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### **Patient Counseling Information**

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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ERIC R BRODSKY  
05/21/2012

LAURIE B BURKE  
05/21/2012



- Manufacturing process analysis
- Other

Dissolution profiles generated using the proposed dissolution method are highly variable and provide for complete drug release over an extended time frame (b) (4) for a drug product designated as immediate release. The test method also does not comply with USP recommendations for enzyme concentrations and utilizes high amounts of surfactant. These issues present a regulatory challenge for actions on post approval CMC changes affecting product performance, where a robust dissolution test method is critical. A suboptimal dissolution test method also introduces an undesired risk for variability in batch-to-batch product performance.

2. Describe the particular review issue and the goal of the study.

The goal of the study is to optimize the current dissolution test method and acceptance criteria for improved quality assurance of batch to batch consistency.

3. [OMIT — for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay Sterility Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The study will evaluate the utility of a two-tiered dissolution method to address capsule rupture efficiency issues, identify different method parameters that allow for enzyme use in accordance with USP guidelines, and identify a more suitable surfactant that can be used at a lower concentration, ideally <2%. At the end of the study, the Applicant will make a proposal to FDA for a final dissolution test method for quality control. Once an agreement is reached between FDA and the Applicant on a final dissolution test method, the final accepted test method will be used to define acceptance criteria in accordance with FDA Guidelines for IR products (i.e., *one or two-point specification, as appropriate*) to improve product quality assurance for this important drug.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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MATTHEW E WHITE

05/16/2012

PMC sent to sponsor on 4/27/12. Sponsor agreed to the PMC in their submission dated 5/4/12.

TATIANA OUSSOVA

06/08/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion/Division of Consumer Drug  
Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 8, 2012  
**To:** Matthew White, RPM, DDDP  
**From:** Lynn Panholzer, PharmD, DPDP  
Sheetal Patel, PharmD, DCDP  
**Subject:** NDA# 021951  
CIP-ISOTRETINOIN (isotretinoin) Capsules

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As requested in your consult dated January 30, 2012, OPDP has reviewed the draft labeling (package insert [PI], Medication Guide [MG], carton/container labeling) for CIP-ISOTRETINOIN (isotretinoin) Capsules. DPDP reviewed the proposed, substantially complete, marked-up version of the PI provided by DDDP via e-mail on April 20, 2012, and the draft carton/container labeling submitted by the applicant on April 26, 2012, available in the EDR. DCDP reviewed the proposed MG previously marked up by the Division of Medical Policy Programs.

OPDP's comments on the PI and MG are provided directly in the attached copy of the labeling.

OPDP has the following comments on the carton/container labels, also attached:

1. In the marked-up version of the draft PI, the phrase [REDACTED] (b) (4) [REDACTED] has been deleted from the Psychiatric Disorders section (5.4). However, the section of the draft container label titled, "Mental problems and suicide" still states "No one knows if isotretinoin caused these problems or behaviors or if they would have happened even if the person did not take isotretinoin." In light of the revision to the draft PI, is the statement on the container label still accurate?
2. The container labeling states:

Other important information is found in the Medication Guide and in the booklets from your doctor:

{

- Common side effects that are not serious . . .

We acknowledge that the bulleted statement is also presented in the Accutane container label. However, we believe that it minimizes the risks of the drug. Therefore, we recommend deleting this statement.

If you have any questions regarding the PI or carton/container labels, please contact Lynn Panholzer at 6-0616 or at [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov). If you have any questions regarding the MG, please contact Sheetal Patel at 6-5167 or at [Sheetal.Patel@fda.hhs.gov](mailto:Sheetal.Patel@fda.hhs.gov).

32 Pages of Draft Labeling have been Withheld in Full as  
B4 (CCI/TS) Immediately Following this Page

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/s/  
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LYNN M PANHOLZER  
05/08/2012

SHEETAL PATEL  
05/08/2012



## **INTRODUCTION**

On November 29, 2011, Cipher Pharmaceuticals Inc., submitted a Complete Response to the Division of Dermatology and Dental Products in response to the April 25, 2007, Approvable Letter for CIP-isotretinoin capsules. Cipher Pharmaceuticals is seeking approval of the 10, 20, 30 and 40 mg capsules of cip-isotretinoin for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

The Division of Dermatology and Dental Products (DDDP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the pregnancy and nursing mothers sections in the cip-isotretinoin labeling.

The PMHS-MHT review provides suggested revisions and re-ordering of existing information related to pregnancy and nursing mothers in the cip-isotretinoin labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## **BACKGROUND**

### **CIP-isotretinoin**

The active ingredient of cip-isotretinoin is the oral retinoid isotretinoin. The innovator product, Accutane, was available in the United States until 2009 when it was discontinued from the market by the sponsor. Isotretinoin is currently available in the United States under generic brand names.

Isotretinoin is a known human teratogen. Isotretinoin is available only through a restricted distribution program called iPLEDGE which is part of the product's Risk Evaluation and Mitigation Strategy (REMS).

### **Regulatory History:**

The original NDA for cip-isotretinoin was submitted on July 1, 2005, and was followed by an Approvable letter on May 1, 2006 due to multiple deficiencies. On October 26, 2006, the sponsor submitted a Complete Response (CR) to the May 1, 2006, Approvable letter but only addressed one of the deficiencies in the May 1, 2006, Approvable letter. The sponsor received another Approvable letter on April 25, 2007. On June 28, 2007, the sponsor submitted a Formal Dispute Resolution to the Agency which was followed by multiple discussions between the Agency and the sponsor regarding the Special Protocol Assessment (SPA) for the sponsor's Phase 3 trial in which agreements were reached.

## **DISCUSSION AND CONCLUSION**

### **Pregnancy and Nursing Mothers Labeling**

Until the Pregnancy and Lactation Labeling Rule (PLLR) publishes, the Maternal Health Staff is using a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. The PMHS-MHT labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008).

Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

### **PMHS-MHT LABELING RECOMMENDATIONS**

PMHS-MHT discussed labeling at a meeting with DDDP on April 18, 2012 and again with DDDP and the Division of Risk Management (DRISK) on April 19, 2012. The attached labeling reflects agreed upon labeling revisions to pregnancy and nursing mothers.

Some PMHS-MHT recommendations, based on the intent of the pending pregnancy and lactation labeling rule [PLLR], were not included at this time because of the possible impact of such changes on other isotretinoin products and the iPLEDGE program.

- PMHS-MHT recommended that the iPLEDGE language be moved to a new Section 8.6 Females of Reproductive Potential however, after discussions with DRISK it was learned that the current recommendation is for any REMS language (iPLEDGE) to remain in Section 5 WARNINGS and PRECAUTIONS following the WARNINGS and PRECAUTIONS for the safety concern contained in the REMS. PMHS-MHT agrees with the current placement but suggests that placement of this type of information be re-addressed when the final PLLR is issued.
- The term ‘females of childbearing potential’ was retained [REDACTED] (b) (4) [REDACTED] because the term ‘females of childbearing potential’ is the current language used in the iPLEDGE program.

The language describing iPLEDGE was not reviewed at this time. PMHS-MHT recommends a review and update of the iPLEDGE language for all isotretinoin labels as part of revisions under PLLR. PMHS-MHT also recommends a larger discussion of the labeling for all isotretinoin products in the future to assure consistency of application of the PLLR across labels.

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### **APPENDIX A: PMHS – Recommended Revisions for Isotretinoin Labeling**

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/s/  
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CARRIE M CERESA  
05/02/2012

MELISSA S TASSINARI  
05/02/2012

LISA L MATHIS  
05/10/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: April 30, 2012

To: Susan Walker, MD  
Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): CIP-ISOTRETINOIN (isotretinoin)

Dosage Form and Route: Capsules

Application Type/Number/Supplement: NDA 21-951

Applicant: Cipher Pharmaceutical Inc.

## 1 INTRODUCTION

On November 28, 2011 Cipher Pharmaceutical Inc. submitted a Complete Response (CR) in response to the Division of Dermatology and Dental Products (DDDP) Approvable Letter dated April 25, 2007 for CIP-Isotretinoin (isotretinoin) Capsules New Drug Application (NDA) 21-951. The Applicant submission includes clinical study reports for Phase III Study ISOCT.08.01. CIP-Isotertinoin Capsules, NDA 21-951 is a 505(b)(2) application with Accutane (isotretinoin) NDA 18-662 as the Referenced Listed Drug (RLD).

The Applicant's proposed indication for CIP-Isotretinoin (isotretinoin) Capsules is for the treatment of severe recalcitrant nodular acne. On January 24, 2012, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for CIP-Isotretinoin (isotretinoin) Capsules.

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for CIP-Isotretinoin (isotretinoin) Capsules.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DDDP under separate cover.

## 2 MATERIAL REVIEWED

- Draft CIP-Isotretinoin (isotretinoin) Capsules Medication Guide (MG) received on November 29, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on April 23, 2012.
- Draft CIP-Isotretinoin (isotretinoin) Capsules received November 29, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on April 23, 2012.
- Approved Amnesteem (isotretinoin) Capsules comparator patient labeling dated April 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

*Information for People with Vision Loss.* The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- DMPP recommends a comprehensive review of the patient labeling for the isotretinoin class labeling at a future date to bring the Medication Guide up to current patient labeling standards.
- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

18 Pages have been Withheld in Full as Draft  
Labeling Immediately Following this Page

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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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LATONIA M FORD  
04/30/2012

BARBARA A FULLER  
04/30/2012

LASHAWN M GRIFFITHS  
04/30/2012

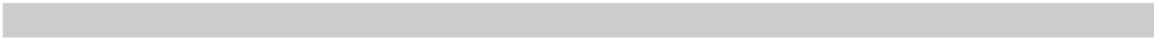
505(b)(2) ASSESSMENT

Application Information		
NDA # 021951	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Isotretinoin Dosage Form: Capsules Strengths: 10 mg, 20 mg, 30 mg, 40 mg		
Applicant: Cipher Pharmaceuticals		
Date of Receipt: 11/29/2011		
PDUFA Goal Date: 5/29/2012		Action Goal Date (if different): 5/15/2012
Proposed Indication(s): Severe recalcitrant nodular acne in patients 12 years of age and older		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 018662 Accutane (isotretinoin) Capsules, 10 mg, 20 mg, and 40 mg.	Boxed Warning Section 1: Indications and Usage Section 2: Dosage and Administration Section 4: Contraindications Section 5: Warnings and Precautions Section 6: Adverse Reactions Section 7: Drug Interactions Section 8: Use in Specific Populations Section 10: Overdosage Section 11: Description Section 12: Clinical Pharmacology Section 13: Nonclinical Toxicology Section 17: Patient Counseling Information

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**BA studies and BE studies under fed condition studies were used to bridge CIP-isotretinoin Capsules to Accutane (isotretinoin) Capsules, the listed drug.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
 YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?  
 YES  NO   
*If "NO," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Accutane (isotretinoin) Capsules	NDA 018662	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
 N/A  YES  NO   
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".  
 If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:  
 a) Approved in a 505(b)(2) application?  
 YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?  
 YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?  
 YES  NO

If “YES”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

**Accutane (isotretinoin) Capsules, 10 mg, 20 mg, 40 mg**

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

**This application provides for a modified formulation, referred to as CIP-isotretinoin, and has different bioavailability under fasted conditions. Consequently, the capsules may be administered without regard to meals, whereas the listed drug is administered with meals.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.*

*If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): The 10 mg, 20 mg, and 30 mg strengths of Accutane are pharmaceutical equivalents.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

<b>PATENT CERTIFICATION/STATEMENTS</b>
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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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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MATTHEW E WHITE  
04/26/2012

**Clinical Consultation**  
**DRUP Track Correspondence No. 290**

**From:** Stephen Voss MD, Medical Officer DRUP

**Through:** Theresa Kehoe MD, Medical Team Leader DRUP  
Audrey Gassman MD, Acting Deputy Division Director DRUP

**To:** Matthew White, RPM, Div. of Dermatology and Dental Products  
Denise Cook MD, Medical Officer DDDP  
Gordana Diglisic MD, Medical Team Leader DDDP

**Subject:** **NDA 021951, CIP-Isotretinoin capsules – review of bone safety data**

**Date consult received:** December 21, 2011

**Date consult completed:** March 30, 2012

**Background:**

Excessive intake of **vitamin A (retinol)** has long been associated with skeletal toxicity. Vitamin A metabolites and synthetic analogs (“retinoids”), including isotretinoin (13-*cis*-retinoic acid), have been developed for the treatment of various skin disorders and malignancies. Like vitamin A, some of these substances have exhibited potential for adverse skeletal effects in animals and humans, including reduced bone size and bone mineral density (BMD), spontaneous fractures, skeletal hyperostosis and ligament calcification, and premature epiphyseal closure. However, the clinical relevance of these findings is mostly unclear, particularly in regard to the relatively limited (in dose and duration) isotretinoin exposures involved in treating acne.

**Accutane® (isotretinoin, NDA 018662)** was approved in 1982 for the systemic treatment of severe recalcitrant nodular acne. A pediatric efficacy supplement (S-043) that was submitted in 2001 addressed the potential bone safety issue. S-043 included a single-arm, open-label study (M01513) of 217 adolescents with acne (age 12-17 y/o, mean 15.1 y/o, 63% male) who received a 16-20 week treatment of Accutane 1 mg/kg/day. DXA scans showed that from baseline to post-treatment, there was a significant 1.4% increase in mean lumbar spine BMD but a significant ( $p=0.03$ ) *decrease* of 0.5% in mean femoral neck BMD, and little change in total hip BMD. There was 1 subject (0.5%) with a significant decrease ( $>4\%$ ) in BMD at the lumbar spine and 9 subjects (4.5%) with significant decrease ( $>5\%$ ) in BMD at the total hip. After adjustment of BMD data for height and weight, these percentages increased to 7.9% and 10.6%. Follow-up of these subjects conducted up to 11 months after treatment end showed that about half recovered to baseline or above. (DiGiovanna 2004)

Reviewers of this study were concerned about the findings because adolescents normally experience substantial increase in BMD over time, in part due to bone growth and hormonal changes, and the study had no placebo group to provide comparison. Although the pediatric supplement was approved, labeling included warnings about the potential

for bone loss, hyperostosis and premature epiphyseal closure, and a statement that musculoskeletal effects may be greater with long-term or high-dose therapy or multiple courses of therapy. Accutane (and numerous generics) are approved for use in patients  $\geq$  12 y/o, and the PI indicates that use in younger children has not been studied.

### **CIP-Isotretinoin**

Accutane is poorly absorbed under fasting conditions, due to high degree of lipophilicity of isotretinoin, and should be taken with food. CIP-Isotretinoin is being developed (IND 064927) by Cipher Pharmaceuticals as an alternate formulation that can be taken without regard to meals and provides more consistent drug exposure. CIP-Isotretinoin is bioequivalent to Accutane under high-fat-fed conditions, and bioavailability is reduced only 30% under fasting conditions, vs. 70% lower with Accutane. Therefore potentially, overall drug exposure may be higher with CIP-Isotretinoin relative to Accutane when patients skip meals.

**NDA 021951** was submitted in July 2005 as a 505(b)(2) application. In May 2006 and April 2007, DDDP issued approvable letters, based on inadequate evidence that the PK differences between CIP-Isotretinoin and Accutane would be clinically insignificant. Cipher was asked to conduct a clinical safety and efficacy trial comparing the two products, including data on BMD and epiphyseal closure, regarding which DMEP/DRUP provided consultation on study design. Agreement was reached in April 2009 on the terms of a Special Protocol Assessment phase 3 trial. This trial, ISOCT.08.01, has now been completed, and the full report was submitted on November 29, 2011 as a Complete Response. DRUP is requested to evaluate the bone-related data from this trial, the adequacy of the methodology, and the adverse event profile, and to comment on relevant sections of the label.

**ISOCT.08.01** was a phase 3, double-blind, randomized trial comparing CIP-Isotretinoin with active-control generic isotretinoin, which was conducted at 49 U.S. and Canadian sites. The trial enrolled 925 male and female subjects age 12-54 y/o with severe recalcitrant nodular acne, who were otherwise healthy and retinoid-naïve. Specific exclusion criteria potentially related to bone disorders were the following:

- adolescents (age 12-17 y/o) with baseline BMD Z-score  $< -2$
- adolescents with baseline serum 25(OH)vitamin D  $< 20$  ng/mL
- rickets or other 25(OH)D depletion disease or phosphate metabolic disease
- HLA-B27-related disease
- rheumatoid arthritis
- severe scoliosis ( $> 15^\circ$  Cobb angle)
- history of back surgery/injuries
- cervical hyperostosis at baseline
- use of corticosteroids, bisphosphonates, phenytoin, Depo-Provera

The subjects (396 adolescents, 529 adults) were randomized to receive a standard 20-week course of treatment consisting of CIP-Isotretinoin (n=464) or generic isotretinoin (n=461) capsules at a dose of  $\sim 0.5$  mg/kg/day for the initial 4 weeks followed by  $\sim 1.0$  mg/kg/day for 16 weeks, followed by an additional 4 weeks of post-treatment

observation. Treatments were given in two divided doses daily with meals. Clinic visits occurred at screening, baseline, and weeks 2, 4, 8, 12, 16, 20, and 24 (post-treatment). Overall, 88% of subjects completed the treatment phase (week 20 visit).

The study report indicates that the number of acne lesions (the primary efficacy endpoint) was reduced by ~90% with both products; Ciper claims that all efficacy and safety results were equivalent.

### **Bone substudy**

The objective of this substudy was to compare CIP-Isotretinoin and control isotretinoin with respect to changes in BMD and (in adolescents) bone age, in order to establish that bone safety of the new product is not inferior.

As requested by FDA and specified in the protocol, all adolescent (age 12-17 y/o) subjects in the overall study, and a subset of adult (age 18-54 y/o) subjects, also participated in the bone substudy. Additional exclusion criteria applicable to this substudy were the following:

- <3 vertebrae between L1 and L4 evaluable by DXA
- Metal prosthesis in the spine, hip, or femur
- Adults with baseline serum 25(OH)vitamin D levels < 20 ng/mL
- Female patients receiving hormone replacement therapy (oral contraceptives [OCs] were allowed, except for micro-dose progesterone and OCs with anti-acne indications)

**BMD assessments:** The International Society for Clinical Densitometry (ISCD) recommends Lumbar Spine and Total Body Less Head (TBLH) as the most accurate and reproducible skeletal sites for DXA in children and adolescents. The hip, a standard measure in adults, is considered by ISCD to be less reliable “in growing children” because of potential inconsistencies in patient positioning (esp. malrotation of leg), which is in part related to less developed skeletal landmarks (esp. lesser trochanter). However, total hip and femoral neck are widely used in pediatric DXA, and extensive normative data for these and other skeletal sites have been developed in the Bone Mineral Density in Childhood Study.(Kalkwarf 2007) Compared to the lumbar spine, DXA precision error (%CV) is often somewhat higher at the hip due to greater potential variance in patient positioning, particularly at the femoral neck due to its smaller area.

In study ISOCT.08.01, BMD measurement in both adolescents and adults consisted of DXA of PA lumbar spine and left hip. The initial protocol specified that adolescents would also undergo TBLH scan, however it was found that this type of scan was unavailable at most study sites, and it was deleted from the protocol.

**Reviewer comment:** *Although the Sponsor was previously requested to submit any TBLH data collected, none were included in the NDA. These data were requested in an IR on 2/17/12; in response the Sponsor reiterated their previous statement that TBLH was not performed because it was unavailable at most sites. The DXA datasets initially submitted included only BMD, and not the associated parameters of BMC (bone mineral content)*

and BA (bone area), which are frequently used in pediatrics. In response to an IR, the Sponsor added BMC and BA data to the “FA” dataset and resubmitted it on 3/23/12.

The baseline DXA was conducted between screening (within 45 days of baseline in most cases) and baseline. The end of treatment (EOT) scan was conducted at week  $20 \pm 7$  days. The endpoints of interest were percent change (baseline to EOT) in spine, total hip and femoral neck BMD, as well as change from baseline in corresponding Z-scores (adolescents) or T-scores (adults). For adolescent subjects meeting certain FDA-specified criteria for bone loss at EOT ( $\geq 4\%$  BMD decline at spine or total hip, or  $\geq 5\%$  BMD decline at femoral neck), DXA images were reviewed by radiologists for quality (particularly hip positioning). Appendix 14.7 (Radiology Narratives) of the CSR includes these interpretations, with an assessment of the significance of the BMD changes and rationale for conducting or not conducting additional follow-up scans. Most of these adolescents with bone loss at EOT underwent a third, short-term follow-up scan within 4 months after EOT. Based on the radiologist assessments, only a few subjects also underwent a longer-term follow-up scan (up to 11 months post-treatment); data from these delayed scans were not included in the “ADBMD” dataset, though the narratives provide minimal information.

All aspects of DXA scans were coordinated centrally by (b) (4) which provided local centers with instructions and training, including regarding cross-calibration and instrument quality control. These procedures are outlined in a DXA procedures manual provided in response to an IR. Each site was required to perform short-term precision testing using a (b) (4) measured 10x on each machine. These phantom data were provided (in response to IR) and show that instrument precision error averaged  $\sim 0.2\%$  across all sites and was  $\leq 0.51\%$  at every site (except for 3 sites where no phantom data were collected). (b) (4) (52%) or (b) (4) (48%) scanners were used, and each subject was to have all scans on the same machine. Pediatric scan modes with more sensitive bone edge detection were used as appropriate for size and body weight. The report lists the DXA hardware and software used at each study site, however the datasets do not indicate whether a pediatric scan mode was utilized. All DXA personnel were blinded to treatment group assignment. The manufacturers’ normative databases proprietary to the equipment were used to generate Z- and T-scores.

**Reviewer comment:** *These DXA procedures appear to be adequate.*

In children and adolescents, Z-scores use age- and gender-specific reference data to compare an individual’s BMD to his or her peers. A Z-score of  $\leq -2$  is generally considered to represent “low BMD for chronologic age”, though it may not indicate a significantly increased risk for fracture and is not recommended to be used by itself to diagnose any condition (e.g. osteoporosis), rather to be considered within the patient’s clinical context. In addition to age and gender, BMD is influenced by skeletal growth and sexual maturation, the timing of which varies greatly between individuals, especially around puberty. Therefore in addition to BMD, the study included assessments of adolescents’ bone age, Tanner stage of pubertal maturity (by self-assessment) and age of

menarche (girls). These measures were to help rule out an effect of the drug on sexual maturation, and also to help with interpretation of the BMD and bone age data.

**Bone age** in adolescents was determined by the most common method, which uses X-rays of the left wrist/hand compared to reference images in the Greulich and Pyle atlas. In this method, each film, specifically the appearance of the epiphyses and morphology of the bones, is matched to a reference image which assigns that subject's "bone age". An accompanying table gives the SD in months that the bone age represents in relation to the subject's chronologic age. During adolescence, this table indicates that 1 SD in bone age is ~10-13 months. A difference between bone age and chronological age of greater than 2 SD is widely considered potentially significant as an indicator of rapid epiphyseal closure. For study ISOCT.08.01, an increase in bone age  $> 1.5$  SD was considered to represent potential acceleration of bone age. In addition, each image was assessed for "epiphyseal closure", defined as closure of the distal radius epiphysis, which is the last epiphysis in the wrist or hand to close. These X-ray interpretations and calculations were performed centrally by up to 3 radiologists blinded to treatment group at (b) (4)

**Follow-up of subjects with potential bone toxicity** was the topic of very extensive discussions during protocol design; eventually the Sponsor agreed that subjects with any of the following changes from Baseline to EOT would have appropriate follow-up:

- Adults with  $\geq 7\%$  BMD loss at any site would be flagged for follow-up BMD at 12 months or until return to baseline
- Adolescents with increase in bone age  $> 1.5$  standard deviations during the study were to be followed episodically until epiphyseal closure, and final height recorded

FDA also requested, but Sponsor did not agree, that the following adolescent groups would undergo follow-up DXA until return to baseline or for up to 12 months:

- Adolescents with  $\geq 4\%$  BMD loss at spine or total hip
- Adolescents with  $\geq 5\%$  BMD loss at femoral neck
- Adolescents with EOT Z-score of  $< -2.0$  at spine, total hip or femoral neck

This remained an area of non-agreement, the Sponsor's rationale being that precision error of DXA is such that these 3 criteria would require excessive numbers of adolescents to undergo repeat studies (with radiation exposure) because of apparent changes that were due only to random variation. When the study was eventually conducted, most adolescents meeting one of these criteria did undergo a follow-up DXA, however almost all of these were within 2-3 months of the end of treatment and did not show return to baseline (see below).

## **Results - Adolescents (age 12-17 y/o)**

### **Demographics – Adolescents**

As noted in **Table 1**, majorities of the adolescent subjects were in the categories of white, male, older (age 15-17 y/o), and Tanner stages 4-5. The mean age was 15.4 y/o for males and 15.2 y/o for females. Baseline BMD Z-scores were on average  $\sim 0.5$  SD above subjects' peer groups, reflecting their general good health. About 79% of subjects were U.S. and 21% Canadian.

**Table 1. Demographic and baseline characteristics – Adolescents**

	<b>CIP-Isotretinoin (N = 204)</b>	<b>Active control (N = 192)</b>	<b>Overall (N = 396)</b>
<b>Age (years)</b>			
Mean	15.3	15.4	15.4
Median	16.0	16.0	16.0
<b>Age group</b>			
12-14 y/o	30%	21%	26%
15-17 y/o	70%	79%	74%
<b>Gender</b>			
Male	80%	80%	80%
Female	20%	20%	20%
<b>Tanner Stage*</b>			
<b>Males – card 1</b>			
1-3	6%	11%	8%
4	60%	55%	58%
5	34%	33%	33%
<b>Males – card 2</b>			
1-3	7%	4%	5%
4	54%	48%	51%
5	38%	46%	42%
<b>Females– card 1</b>			
1-3	18%	8%	13%
4	60%	59%	60%
5	23%	33%	28%
<b>Females – card 2</b>			
1-3	12%	10%	11%
4	38%	44%	41%
5	50%	46%	48%
<b>Race</b>			
White	98%	95%	96%
Asian	1%	3%	2%
Other	1%	2%	2%
<b>Ethnicity</b>			
Hispanic	10%	6%	8%
Non-Hispanic	90%	94%	92%
<b>Hormonal contraceptive use**</b>	43%	49%	46%
<b>Weight – mean (kg)</b>	69.7	70.9	70.3
<b>25(OH) vitamin D (mean, in ng/mL))</b>	30.0	31.0	30.5
<b>L-spine Z-score (mean)</b>	0.397	0.327	0.366
<b>Total hip Z-score (mean)</b>	0.533	0.555	0.543
<b>Femoral neck Z-score(mean)</b>	0.543	0.585	0.563
* For males, Card 1 assessed penis size and Card 2 assessed pubic hair growth. For females, Card 1 assessed breast development and Card 2 assessed pubic hair growth.			
** Females only			
Source: Table 14.3.3.6.3, App. 16.7; ADBMD			

### **Concomitant medications – adolescents**

A few subjects used systemic glucocorticoids for various conditions during the study, but apparently only for several days or less in almost all cases. One adolescent (each) used depakote, Trileptal or clonazepam throughout the study for various conditions. As noted above and allowed under the protocol, hormonal contraceptives were used by almost half of the female subjects.

### **DXA Results – Adolescents**

As specified in the protocol, all 396 adolescent subjects underwent DXA scans at baseline. EOT (week-20) DXA scans were conducted on 156 out of 204 subjects (76.5%) assigned to CIP-Isotretinoin, and 150 out of 192 subjects (78.1%) assigned to control. Subjects who underwent EOT scans were similar in baseline Z-score to those who did not have an EOT scan. For most subjects meeting prespecified criteria for bone loss (see above), a third, short-term follow-up scan was also done; 72% of such scans were performed within 1 month of EOT, and 95% within 2 months. A small number of longer-term follow-up scans were also done.

The Applicant analyzed BMD changes separately for subjects whose scans were performed on (b) (4) equipment. These DXA machines use different technology for bone edge detection, therefore their results are not interchangeable: BMD measurements (b) (4), are generally about 12% higher for lumbar spine and 2% higher for total hip. Despite this difference, BMD data from both types of machine can be, and usually are, combined for analysis, because calculations of the primary endpoint of percent change in BMD are unaffected (provided that every subject has each of their scans performed on the same machine, as was the case in this study). The other endpoints of interest, Z-scores and T-scores, are also unaffected by this issue because they are based on normative databases that are machine-specific. Therefore this reviewer combined all data (b) (4) for analyses.

**Lumbar spine BMD** increased ~1.5-2.0% from baseline over the 20 weeks of treatment in the adolescents. (**Table 2**) Bone mineral content (BMC) increased by a slightly higher percentage related to a mean increase in measured lumbar spine bone area of 1.04%. Accounting for the expected BMD gains in this age group, however, there was a slight decline from baseline in mean Z-score of -0.053 that was statistically significant ( $p=0.0003$ ). The control group had slightly greater BMD gains than the CIP-Isotretinoin group, with no statistically significant difference between these treatments.

**Table 2. Lumbar Spine BMD, BMC and Z-score by treatment group – Adolescents (age 12-17 y/o)**

	CIP-Isotretinoin (N = 204)	Active control (N = 192)	Overall (N = 396)
<b>Baseline</b>			
N	204	192	396
BMD, Mean(SD) (g/cm <sup>3</sup> )	1.084 (0.152)	1.081 (0.144)	1.083 (0.148)
Z-score, Mean (SD)	0.397 (1.107)	0.327 (1.073)	0.366 (1.090)
<b>Week 20 (End of treatment)</b>			
N	154	149	305
<b>Mean (SD) %Change in BMD from BL</b>	<b>1.559</b> (3.067)	<b>2.042</b> (2.604)	<b>1.779</b> (2.853)
p-value: CIP vs. control*	0.1411		
range	-4.46, 14.85	-3.83, 11.51	-4.46, 14.85
# w/ increased BMD	110	114	224
# w/ decreased BMD	46	35	81
Mean (SD) %Change in BMC from BL	2.755 (4.346)	3.045 (3.250)	2.901 (3.833)
<b>Mean (SD) Change in Z-score from BL</b>	<b>-0.073</b> (0.263)	<b>-0.032</b> (0.237)	<b>-0.053</b> (0.251)
p-value: Z-score for CIP vs. control*	0.1567		
# w/ Z-score < -2 at EOT	1	0	1
*p-value from 2-sample paired t test Source: ADBMD			

Only one subject (#37010), a 16 y/o male assigned to CIP-Isotretinoin, experienced  $\geq 4\%$  lumbar spine BMD decline at week 20 (-4.46%), which was unchanged at week 28 (-5.01%). The radiologist's interpretation notes that the baseline image showed some curvature that was not present on the 2 follow-ups, nevertheless they did recommend a 1-year follow-up of lumbar spine BMD in this one subject (which was not reported in the NDA). This subject also experienced substantial BMD decline at the other skeletal sites (-3.60% total hip, -8.97% femoral neck).

Another subject (#43039), a 15 y/o male assigned to active control, had an "end of treatment" scan at week 17 showing decline (-4.52%) at lumbar spine, which improved to -1.73% at week 22.

No subject exhibited a significant (defined as  $> 1$  SD) decline from baseline lumbar spine Z-score.

**Reviewer comment:** *These lumbar spine DXA results in adolescents are fairly reassuring. There may be a slight negative effect of isotretinoin on overall spine BMD gains, because the mean Z-score declined. The clinical significance would probably be minor, as the proportion of subjects with substantial short-term bone loss at this skeletal site was very low with either treatment.*

**Total hip** bone is less metabolically active than lumbar spine (more cortical, less trabecular bone) and is expected to show lesser changes over a given time period. Over the 20 weeks of this study, mean total hip BMD showed minimal change from baseline which was statistically insignificant. Total hip BMC and bone area increased by 0.2% and 0.3% respectively. Because of the expected BMD increase for this age group, there was a modest but highly significant ( $p < 0.0001$ ) decline from baseline in Z-score which applied to each treatment group (-0.122 SD for CIP-Isotretinoin and -0.095 SD for control), with no statistical difference between these two groups. (**Table 3**)

**Table 3. Total Hip BMD, BMC and Z-score by treatment group – Adolescents (age 12-17 y/o)**

	CIP-Isotretinoin (N = 204)	Active control (N = 192)	Overall (N = 396)
<b>Baseline</b>			
N	204	192	396
BMD, Mean(SD) (g/cm <sup>3</sup> )	1.086 (0.139)	1.088 (0.140)	1.087 (0.139)
Z-score, Mean (SD)	0.533 (0.997)	0.555 (1.064)	0.543 (1.028)
<b>Week 20</b>			
N	151	149	300
<b>Mean (SD) %Change in BMD from BL</b>	<b>-0.280</b> (2.576)	<b>0.002</b> (2.443)	<b>-0.140</b> (2.510)
p-value: CIP vs. control*	0.33		
Median	0.089	-0.236	
range	-12.309, 9.294	-9.290, 7.746	-12.309, 9.294
# w/ increased BMD	77	67	154
# w/ decreased BMD	74	82	156
Mean (SD) % Change in BMC from BL	0.290 (3.893)	0.105 (3.763)	0.199 (3.824)
<b>Mean (SD) Change in Z-score from BL</b>	<b>-0.122</b> (0.258)	<b>-0.095</b> (0.231)	<b>-0.109</b> (0.245)
p-value: Z-score for CIP vs. control*	0.2867		
# w/ Z-score < -2 at EOT	3	1	4
*p-value from 2-sample paired t test Source: ADBMD			

Moreover, there were 17 out of 300 subjects (5.67%; 11 CIP-Isotretinoin, 6 control) who met the prespecified criterion of a post-baseline total hip BMD that was  $\geq 4\%$  below baseline, indicating significant bone loss. (**Table 4**) Three of these subjects (#11020, #15038, #46017) also had significant ( $> 1$  SD) decline from baseline in total hip Z-score (range -1.009 to -1.457). Only 1 of these 17 subjects was a girl (#05027); note, however, that only 20% of all adolescent subjects were girls. The mean age of these 17 subjects was 14.8 y/o, somewhat younger than the overall group mean of 15.4 y/o.

As noted in **Table 4**, all except 2 of these 17 subjects underwent an additional post-treatment scan, most of these within 1-2 months after EOT. The end-of-treatment and short-term follow-up ( $\leq 4$  mos post treatment) scans generally agreed with each other (%)

change from baseline within ~1.5% in all subjects except one) in showing substantial decline from baseline BMD. There was no apparent trend toward BMD recovery for these 17 subjects within this time frame; most actually had further BMD decline after end of treatment, including on 2 of 3 scans performed between 2-4 months post-EOT. Most of these subjects remained below the -4.0% threshold in short-term follow-up, with none returning to pre-treatment baseline.

Based on these results and review of the images, the radiologists recommended only 5 of these 17 subjects to have a longer-term follow-up (up to 11 months post-treatment) DXA. These delayed scans showed some improvement though one subject remained well below his baseline (-6.3%) at 11 mos post-treatment. The delayed scans were not included in either the ADBMD dataset or in the CSR analyses; the data in the 2 far-right columns of **Table 4** were extracted from the narratives by this reviewer.

**Table 4. Adolescent subjects with a decline in total hip BMD  $\geq 4\%$  from baseline**

Subject #	Treatment group	Initial post-treatment DXA* (~EOT)		Short-term ( $\leq 4$ mos) follow-up DXA*		Longer-term ( $> 4$ mos) follow-up DXA**	
		% change from BL	Study day	% change from BL	Study day	% change from BL	Study day
04034	CIP	-3.62	141	-4.55	257		
05027	CIP	-2.68	146	-4.12	159	-1.6	341
08024	CIP	-4.40	134			+0.7	380
11004	CIP	-4.40	164	-5.65	232		
11020	CIP	-9.79	142	-10.27	210	-6.3	479
12015	CIP	-4.98	169				
15038	CIP	-12.31	148	-12.23	168		
18019	CIP	-5.74	136	-4.19	171	+4.2	355
28038	CIP	-5.88	140	-6.72	155		
29014	CIP	-4.58	149	-6.20	177		
43058	CIP	-5.27	130	-6.50	151		
08018	control	-7.04	125	-3.93	149		
15010	control	-4.79	150	-3.15	262		
15043	control	-4.19	155	-5.15	169		
22011	control	-4.35	140	-4.89	161		
44012	control	-6.59	139				
46017	control	-9.29	144	-10.41	170	***	332

Study day = day from initiation of treatment  
\*Source: ADBMD dataset  
\*\* Source: CSR Narratives/ Appendix 14.7, M5.3.5.1.3  
\*\*\* Scan performed, however result unclear from description in Narratives

According to the narratives and the CSRs, none of the DXA data on any of these 17 subjects are considered by the Sponsor to have any clinical significance, nor do they warrant any additional follow-up. Their stated rationale includes the following:

- Although these cases were identified for potential follow-up based on the FDA’s criterion of  $\geq 4\%$  BMD decline, the interpreting radiologists applied their preferred threshold of  $\geq 5\%$  for “Least Significant Change” for total hip DXA (see below), and in some cases they arbitrarily considered changes beyond 5% to be “almost certainly normal”.

- They state (as this Sponsor has previously contended) that hip DXA in any pediatric population is inherently “unreliable and inconsistent”, primarily because positioning of the hip is more likely to be inconsistent in this population, compared to adults. In this regard, they state that in 6 of these subjects (#04034, #05027, #15043, #18019, #28038, and #44012) the images show a change in position (e.g. rotation) between baseline/post-treatment scans which may have created the appearance of BMD decline. However, images of the hip scans from the remaining 11 subjects (including those with the largest BMD declines) were interpreted as “technically adequate”, with no mention of discrepancies in hip positioning.
- In one subject (#15038), femoral neck BMD increased by 3.8% and 2.5% on the 2 post-treatment scans, therefore a significant decline in total hip (-12.31%, -12.23%) was assumed to be unreliable.
- In 2 subjects (#11020 and #15043), BMD decline was attributed to the subjects’ height being > 90<sup>th</sup> percentile, and it was speculated that rapid growth could “result in a transient decrease in measured BMD”.
- In the 4 subjects with extended follow-up data at 6-11 months post-treatment (R-hand columns in the table), 3 improved to near or above baseline BMD. The upward trend in the other (#11020) was considered to indicate that there would be no “lasting change” in the subject’s BMD.

**Reviewer comment:**

*This reviewer finds these arguments unconvincing. The Sponsor claims that the BMD declines from baseline to EOT in these 17 subjects were caused primarily by random variation of DXA, due to hip positioning and/or inherent machine imprecision. This contention is based primarily on parts of the ISCD Position Statement on pediatric DXA (Baim 2008, Gordon 2008). This ISCD document states that precision error (which multiplied by 2.77 yields the 95%-confidence “Least Significant Change” or LSC) should be measured by each DXA facility to calculate its unique LSC to use in determining significance of individual subject BMD changes. The ISCD document also states that the “minimum acceptable precision for an individual technologist” is 1.8% for total hip (which yields LSC = 5.0%). The DXA narratives in this NDA cite this statement as an indication that changes in total hip BMD <5% are insignificant, however this figure was only intended by ISCD to be a minimum DXA quality standard and not a typical result.*

*As an example of more typical pediatric DXA precision data, the same ISCD Position Statement cites data from the Bone Mineral Density in Childhood Study, which found that for adolescents age 14-16 y/o, precision error (%CV) was similar to adult values from the literature at all skeletal sites, including total hip precision error of 0.69%. (DXA was less precise i.e. higher %CV in younger children.) (Shepherd 2004) Thus, the 95%-confidence LSC for total hip BMD (precision error x 2.77) would be only 1.91% - far less than the changes seen in the 17 adolescents in the table. If DXA precision in study ISOCT.08.01 were comparable to that cited as typical by ISCD, one would predict that 7.5 out of the 300 adolescent subjects would appear to have BMD decline >1.91% if DXA imprecision were the only factor; in actuality 60 out of 300 subjects had changes beyond this threshold.*

*Aside from these considerations, there are other important reasons not to dismiss the BMD changes in these 17 subjects as insignificant. Most compelling is the high degree of consistency between the end-of-treatment and short-term follow-up scans, which confirmed substantial bone loss in each subject tested. Furthermore, healthy adolescents experience a mean annual increase in total hip BMD of ~3.4-8.6% (boys) (Kalkwarf 2007). A typical study subject should have experienced an increase of nearly half this amount during the study; such a trend should markedly diminish the number of subjects with measured declines caused by DXA imprecision.*

*Therefore, it appears very likely that about 5% of adolescent study subjects experienced significant hip bone loss (BMD decline  $\geq 4\%$ ). The overall study population did not show a significant BMD decline (overall mean decline was only 0.14%), though as noted an increase would have been expected in healthy teenagers. It is unclear why the subset of 17 subjects was more susceptible to bone loss; the fact that all were boys is notable. It is encouraging that 4 subjects re-evaluated at 6-11 months post-treatment showed at least partial BMD recovery, but more long-term data are needed to determine if isotretinoin-related bone loss is reversible.*

**Femoral neck BMD** showed no mean change from baseline in the control treatment group and a slight mean decline from baseline in the CIP-Isotretinoin group that approached but did not reach statistical significance. For the combined treatment groups, mean BMC and bone area increased by 0.2% and 0.5% respectively. There was a modest but highly significant ( $p < 0.0001$ ) decline from baseline in Z-score which applied to each treatment group (-0.126 SD for CIP-Isotretinoin and -0.082 SD for control). There were no statistical differences between the treatment groups. (**Table 5**)

**Table 5. Femoral Neck BMD, BMC and Z-score by treatment group – Adolescents (age 12-17 y/o)**

	<b>CIP-Isotretinoin</b> (N = 204)	<b>Active control</b> (N = 192)	<b>Overall</b> (N = 396)
<b>Baseline</b>			
N	204	192	396
BMD, Mean(SD) (g/cm <sup>3</sup> )	1.038 (0.163)	1.043 (0.157)	1.040 (0.160)
Z-score, Mean (SD)	0.543 (1.071)	0.585 (1.048)	0.563 (1.059)
<b>Week 20</b>			
N	151	149	300
<b>Mean (SD) %Change in BMD from BL</b>	<b>-0.493 (2.979)</b>	<b>0.046 (3.067)</b>	<b>-0.271 (3.082)</b>
p-value: week 20 vs. baseline*	0.0678	0.67	0.34
p-value: CIP vs. control*	0.1237		
Median	-0.255	-0.059	
Range	-8.971, 10.618	-8.734, 9.592	-8.971, 10.618
# w/ increased BMD	72	71	143
# w/ decreased BMD	79	78	157
Mean (SD) %Change in BMC from BL	-0.259 (4.076)	0.714 (3.731)	0.224 (3.933)
<b>Mean (SD) Change in Z-score from BL</b>	<b>-0.126 (0.265)</b>	<b>-0.082 (0.268)</b>	<b>-0.104 (0.267)</b>
p-value: Z-score for CIP vs. control*	0.1198		
# w/ Z-score < -2 at EOT	3	1	4
*p-value from 2-sample paired t test Source: ADBMD			

There were 20 out of 300 subjects (6.67%; 13 CIP-Isotretinoin vs. 7 control: p=0.26) who had a post-baseline femoral neck BMD that was  $\geq 5\%$  below baseline, including one CIP subject with a -7.31% decline on early withdrawal at day 52. (**Table 6**) One of these subjects (#04032) also showed a significant ( $> 1$  SD) decline from baseline femoral neck Z-score (-1.445 SD). Of these 20 subjects, there were 11 who also met the bone loss threshold ( $\geq 4\%$ ) for total hip, and 1 who met this  $\geq 4\%$  threshold for lumbar spine. There were 18 boys and 2 girls (#05027 and #38026), and the mean age of 14.8 y/o was similar to the group with total hip bone loss, and younger than the overall adolescent population mean of 15.4 y/o.

**Table 6. Adolescent subjects with a decline in femoral neck BMD  $\geq 5\%$  from baseline**

Subject #	Treatment group	Initial post-treatment DXA* (~EOT)		Short-term ( $\leq 4$ mos) follow-up DXA*		Longer-term ( $>4$ mos) follow-up DXA**	
		% change from BL	Study day	% change from BL	Study day	% change from BL	Study day
04034	CIP	-5.64	141	-6.67	257		
05027	CIP	-7.68	146	-8.93	159	-2.4	341
08024	CIP	-6.83	134			+1.1	380
08036	CIP	-6.05	138	-5.83	180		
11004	CIP	-3.87	164	-6.21	232		
11020	CIP	-3.99	142	-5.81	210	0.0	479
11025	CIP	-5.36	143	-3.23	195		
18019	CIP	-7.25	136	-4.11	171	+6.3	355
29014	CIP	-4.32	149	-5.22	177		
34001	CIP	-7.75	157				
37010	CIP	-8.97	139	-6.87	195		
38026	CIP	-7.31	54	-5.03	76		
44010	CIP	-8.90	136				
04032	control	-9.44	156			-5.3	264
08003	control	-7.17	144			+2.7	328
08018	control	-7.82	125	-3.21	149		
15010	control	-5.57	150	-4.47	262		
33011	control	-5.08	158				
44012	control	-8.73	139				
46017	control	-5.27	144	-5.66	170	***	332

Study day = day from initiation of treatment  
\*Source: ADBMD dataset  
\*\* Source: CSR Narratives/ Appendix 14.7, M5.3.5.1.3  
\*\*\* Scan performed, however result unclear from description in Narratives

As with total hip, those subjects who had a short-term follow-up DXA (within 4 mos of end of treatment) were confirmed to have significant femoral neck bone loss in every instance. Although some subjects showed partial improvement on this follow-up scan, others showed further decline. After review, the interpreting radiologist recommended and conducted longer-term follow up DXA in 7 subjects at 4-11 months post-treatment; these showed improvement particularly in the 5 subjects scanned at 6-11 months post-treatment.

The interpreting radiologists considered none of these femoral neck findings to be clinically significant or warranting any additional follow-up, with rationale as noted above regarding total hip data. Citing the ISCD statement regarding “minimum acceptable precision”, they claim that typical femoral neck DXA precision error is 2.5%, therefore LSC is 6.9%, therefore lesser changes  $< 6.9\%$  are insignificant. Also, scans on 5 of these 20 subjects (#04034, #18019, #34001, #44010, and #44012) were cited as showing a significant change in hip positioning between pre- and post-treatment; however, 2 of these (#34001, #44010) were noted by the radiologist to have changes that they acknowledge would tend to cause artifactual *increase* in measured BMD – the opposite of what was found.

**Reviewer comment:**

*As with total hip, there were many subjects with apparent short-term femoral neck BMD decline, which the radiologist and Sponsor attributed to DXA imprecision. The Bone Mineral Density in Childhood Study, cited by ISCD, reported that femoral neck DXA precision error in adolescents age 14-16 y/o was 1.19%. (Shepherd 2004) This figure would result in a 95%-confidence LSC (precision error x 2.77) of 3.3%, less than the changes that occurred in the 20 adolescents listed in the table. Most importantly and similar to the total hip findings, the short-term follow-up scans confirmed the EOT scans, showing femoral neck BMD loss in every subject who was re-tested, and showing no evidence of a trend toward either short-term recovery or regression toward the mean. despite an expected rate of annual increase in femoral neck BMD in this age population of ~3.5-6.6% (boys)(Kalkwarf 2007) Fortunately as with total hip results, the longer-term follow-up scans appeared to show some improvement, but these data were limited.*

**Adolescent subjects with significant bone loss during treatment**

In all, there were 27 out of 300 adolescent subjects (9%) who met one of the prespecified criteria suggested by FDA to indicate potentially significant BMD decline ( $\geq 4\%$  lumbar spine or total hip,  $\geq 5\%$  femoral neck), including 2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck. The Sponsor maintains that the follow-up scans were “normal” (for the varied reasons listed above) in all cases except one: subject #37010, who had substantial bone loss at all 3 skeletal sites. The report conclusions state that this was the only study subject who was asked to return for a one-year follow-up scan.

There were 26 adolescents who met one of the above BMD loss criteria for total hip, femoral neck or both. Within this group, BMD changed in the same (negative) direction at both of these sites in all except 2 subjects. However, lumbar spine BMD simultaneously increased from baseline in 14 of these 26 subjects, and the entire group had a positive mean change of 0.44% (95% CI -0.832, 1.717) in the spine. Only one subject (#37010) had substantial bone loss at all 3 sites.

**Reviewer comment:** *Total hip and femoral neck BMD changes were thus consistent with each other but mostly inconsistent with lumbar spine changes. This disparity between BMD changes of the spine and the hip/femoral neck was previously noted in study M01513 and one other published isotretinoin study (Leachman 1999), in which a possible adverse effect on hip or femoral neck BMD was seen while lumbar spine BMD appeared to be unaffected.*

This group of 27 adolescents with bone loss during isotretinoin therapy was more likely to be male, and somewhat younger, than the overall study population of adolescents. None had any medical history relevant to bone disorders. Their 25-OH-vitamin D levels at baseline (mean 28.15 ng/mL) were slightly less than the overall adolescent group (mean 30.5 ng/mL), however all were  $> 20$  ng/mL per protocol. Their total alkaline phosphatase (AP) serum levels were normal at baseline, and during the study trended downward as did those of most adolescents (due to normal declines with age during adolescence); none exhibited significant increase in AP levels (bone-specific AP was not

measured). The distribution of Tanner stages at baseline for this bone-loss group was similar to that of the overall population. The proportions of this group that experienced an increase in Tanner stage during the study (19% for Tanner stage 1 and 19% for Tanner stage 2) were also very similar to the overall adolescent population (22% and 20% respectively).

All except one subject in this bone loss group (96%) was considered “compliant overall” with study medication, compared to 91% overall. None had a systemic glucocorticoid or anticonvulsant listed as a prior or concomitant medication; 2/27 received ADHD treatments (Concerta, Adderall), about average for the study population.

The mean baseline Z-scores for the subgroup of 27 subjects (0.151 for lumbar spine, 0.568 for total hip, 0.490 for femoral neck) were similar to the overall adolescent population except that the latter had a higher value for lumbar spine (0.366). Following treatment, mean Z-scores for this subgroup declined to -0.078 for lumbar spine, 0.056 for total hip, and -0.083 for femoral neck. All post-treatment Z-scores remained in the “normal” range ( $> -1$ ) for 21 of these 27 subjects.

***Reviewer comment:** Other than a slight preponderance of males and younger ages, this group of 27 adolescents with significant bone loss during treatment had no distinguishing features at baseline that could potentially serve as risk factors for bone toxicity. It is reassuring that because Z-scores for these subjects were generally significantly above average at baseline (like the overall study population), they only declined to around average for their peer groups after treatment, despite the bone loss.*

#### **Adolescent subjects with post-treatment BMD Z-score $< -2$**

This was also one of the prespecified criteria suggested by FDA (but not agreed to by Sponsor) to act as a trigger for DXA follow-up. There was one subject (#12022) who met this criteria for lumbar spine; 4 subjects (#08024, #12022, #28007, #43012) who met this criteria for total hip; and 4 subjects (#08024, #12022, #43012, #44012) who met this criteria for femoral neck. However, in all of these cases, the baseline Z-score was also low ( $< -1.7$ ). Two of these subjects (#08024, #44012) had significant BMD decline during the study (see above); the other 3 (#12022, #28007, #43012) showed minimal change. Three of these subjects (#08024, #12022, #43012) received CIP-Isotretinoin and the other two (#28007, #44012) received control. The study report indicates that radiologists reviewed the scans and data on these subjects and concluded that there is “no indication for a repeat DEXA scan in any of these patients”.

#### **DXA Results - Adolescent Subgroups - Age**

Analysis of subgroups shows that younger adolescents (age 12-14 y/o), compared to older (age 15-17 y/o) had more positive BMD Z-scores at baseline. During the study, younger adolescents had significantly greater increase in lumbar spine BMD compared to older adolescents due to higher age-related background rates of BMD increase. However, the younger subjects also had somewhat greater percent *decline* in hip and femoral neck BMD, as well as greater declines in Z-scores at all 3 skeletal sites during the study.

(Tables 7-8) There did not appear to be any significant differences between the treatment groups in any of these subgroups.

**Table 7. BMD and Z-score by treatment group – age 12-14 y/o**

	CIP-Isotretinoin (N = 61)	Active control (N = 41)	Overall (N = 102)
<b>Baseline</b>			
Lumbar spine Z-score	0.884	0.994	0.928
Total hip Z-score	0.718	0.901	0.790
Femoral neck Z-score	0.620	0.752	0.671
<b>Week 20</b>			
Lumbar spine % change in BMD	2.857	2.390	2.667
Lumbar spine change in Z-score	-0.108	-0.139	-0.121
Total hip % change in BMD	-0.389	-0.334	-0.366
Total hip change in Z-score	-0.284	-0.280	-0.283
Femoral neck % change in BMD	-0.715	-0.385	-0.583
Femoral neck change in Z-score	-0.254	-0.224	-0.242

Source: ADBMD

**Table 8. BMD and Z-score by treatment group – age 15-17 y/o**

	CIP-Isotretinoin (N = 143)	Active control (N = 151)	Overall (N = 294)
<b>Baseline</b>			
Lumbar spine Z-score	0.196	0.145	0.170
Total hip Z-score	0.463	0.462	0.462
Femoral neck Z-score	0.510	0.540	0.525
<b>Week 20</b>			
Lumbar spine % change in BMD	1.138	1.794	1.481
Lumbar spine change in Z-score	-0.052	-0.012	-0.031
Total hip % change in BMD	-0.166	0.120	-0.016
Total hip change in Z-score	-0.085	-0.055	-0.070
Femoral neck % change in BMD	-0.287	0.065	-0.103
Femoral neck change in Z-score	-0.076	-0.057	-0.065

Source: ADBMD

**Reviewer comment:** In the previous study M01513 a similar age-related pattern was seen, i.e. greater decline in total hip and femoral neck BMD in subjects age 12-14 y/o, compared to age 15-17 y/o.

#### **DXA Results - Adolescent Subgroups - Gender**

At baseline, male and female adolescents had similarly above-average Z-scores at all skeletal sites. (Tables 9-10) Following treatment, males had significantly greater increases in lumbar spine BMD compared to females (2.149% vs. 0.396%,  $p < 0.0001$ ).

**Reviewer comment:** This finding is consistent with data showing that boys' BMD gains extend into later adolescence than girls', as shown by the fact that lumbar spine Z-scores showed minor decline during the study that was similar for boys and girls.

In contrast, but also consistent with greater expected gains for boys, total hip and femoral neck BMD declined slightly in both sexes, but boys had significantly greater Z-score declines at these sites than girls: for total hip, -0.129 vs. -0.032 ( $p=0.0073$ ); and for femoral neck, -0.121 vs. -0.047 ( $p=0.0627$ ). As a group, the boys' mean hip and femoral neck Z-scores declined significantly ( $p<0.0001$ ) from baseline; mean change from baseline among the girls was not statistically significant.

**Table 9. BMD and Z-score by treatment group – male adolescents**

	CIP-Isotretinoin (N = 164)	Active control (N = 153)	Overall (N = 317)
<b>Baseline</b>			
Lumbar spine Z-score	0.371	0.301	0.337
Total hip Z-score	0.562	0.548	0.555
Femoral neck Z-score	0.567	0.538	0.553
<b>Week 20</b>			
Lumbar spine % change in BMD	1.962	2.346	2.149
Lumbar spine change in Z-score	-0.064	-0.036	-0.050
Total hip % change in BMD	-0.271	0.024	-0.125
Total hip change in Z-score	-0.145	-0.112	-0.129
Femoral neck % change in BMD	-0.420	0.107	-0.160
Femoral neck change in Z-score	-0.144	-0.096	-0.121

Source: ADBMD

**Table 10. BMD and Z-score by treatment group – female adolescents**

	CIP-Isotretinoin (N = 40)	Active control (N = 39)	Overall (N = 79)
<b>Baseline</b>			
Lumbar spine Z-score	0.538	0.429	0.483
Total hip Z-score	0.449	0.586	0.514
Femoral neck Z-score	0.447	0.777	0.603
<b>Week 20</b>			
Lumbar spine % change in BMD	-0.107	0.883	0.396
Lumbar spine change in Z-score	-0.115	-0.020	-0.066
Total hip % change in BMD	-0.318	-0.084	-0.199
Total hip change in Z-score	0.042	-0.023	-0.032
Femoral neck % change in BMD	-0.797	-0.196	-0.492
Femoral neck change in Z-score	-0.072	-0.022	-0.047

Source: ADBMD

Just under half of the female adolescents used oral contraceptives. During the study, the group that did not use contraceptives experienced slight mean declines in hip and femoral neck BMD and Z-score, while the group using contraceptives remained near baseline (**Table 11**). There were 8 adolescent girls who experienced  $\geq 4\%$  femoral neck BMD decline; 6 of these were non-users of contraceptives including the 2 with  $\geq 7\%$  decline.

**Table 11. BMD and Z-score by baseline oral contraceptive use – female adolescents**

	OCP use (N = 36)	No OCP use (N = 43)	Overall (N = 79)
<b>Baseline</b>			
Lumbar spine Z-score	0.515	0.458	0.483
Total hip Z-score	0.499	0.527	0.514
Femoral neck Z-score	0.641	0.571	0.603
<b>Week 20</b>			
Lumbar spine % change in BMD	0.238	0.530	0.396
Lumbar spine change in Z-score	-0.067	-0.065	-0.066
Total hip % change in BMD	-0.088	-0.300	-0.199
Total hip change in Z-score	-0.012	-0.051	-0.032
Femoral neck % change in BMD	-0.034	-0.905	-0.492
Femoral neck change in Z-score	0.002	-0.092	-0.047
Source: ADBMD			

*Reviewer comment: Z-score results by gender show only a slight overall-group effect of isotretinoin on lumbar spine in either sex, or on hip or femoral neck in girls. Boys, however, experienced more substantial declines in hip and femoral neck Z-scores which, after treatment, were significantly below baseline and also significantly below changes in the girls. It may be that boys in this age group are more vulnerable to the effect of the drug because they are still experiencing rapid BMD accrual, compared to girls in whom this process has already tapered significantly. Contraceptive use also may have partially mitigated negative effects in girls.*

#### **Bone Age Results – Adolescents**

Of the 396 adolescent subjects, 289 (146 CIP-Isotretinoin, 143 control) underwent left wrist/hand X-rays at both baseline and EOT. Most of the bone ages assigned to specific images were at multiples of 6 months, e.g. 15 years, 15 yr 6 mos, 16 years, etc.

For the overall group at baseline, subjects' bone ages were a median of 12.5 months greater than their chronologic age. At end of treatment, subjects' bone ages were a median of 17.5 months greater than their chronologic age ( $p < 0.0001$  for comparison of baseline and EOT). This occurred because chronologic ages advanced a mean of about 5 months, but bone ages advanced a mean of about 10 months; this occurred about equally in both treatment groups.

There were 17 subjects (9 CIP-Isotretinoin, 8 control) who were identified by (b) (4) as showing an increase in bone age of at least 1.5 standard deviations. All of these were subjects whose bone age advanced 24 months from baseline to EOT, except one with an increase of 18 months in bone age and one with an increase of 36 months. When the interval increase in chronologic age is subtracted from this, the increase in bone age relative to chronologic age was 15-20 months, except one with an increase in 12 months and one with an increase of 29 months. (Note that most increases in bone age were at least 12 months, because of the spacing of the reference images used.) Of these 17 subjects, 13 also exhibited closure of the distal radial epiphysis.

These 17 subjects with possibly accelerated skeletal maturation during the study were slightly younger than the overall adolescent study population (mean age 14.7 yr vs. 15.8 yr at baseline), and all except one of the 17 were males. At baseline, their Tanner Card 2 (pubic hair) stage was also slightly younger, with most at stage 4, and fewer at stage 5 than the overall group. (Tanner Card 1 stage was comparable to the overall group, also mostly stage 4.) Following treatment, Tanner stage 1 advanced in 19% of this subgroup, vs. 22% of the overall adolescent population. Tanner stage 2 advanced in 44% of the subgroup, vs. 20% of the overall adolescent population (p=.009, Fisher exact test).

The “radiographs and histories of each of these [17] patients were evaluated to determine if the changes noted were of clinical relevance”, including review of films by 2 treatment-blinded radiologists and, if necessary, adjudication by a third, unblinded radiologist. The precise criteria used for the determination of “clinical relevance” are not stated. Following this evaluation, there were 9 subjects considered to have “clinically relevant” changes: 3 subjects (2 CIP-Isotretinoin and 1 control) with increase in bone age of > 1.5 SD without epiphyseal closure, and 6 other subjects (3 CIP-Isotretinoin and 3 control) with increase in bone age of > 1.5 SD in addition to closure of the radial epiphysis. (Table 12) The protocol states that subjects with >1.5 SD increase in bone age will be “followed episodically until closure, and final height recorded”; the report does not indicate any plans for this.

**Table 12. Adolescents with >1.5 SD increase in bone age – n/N (%)**

	CIP-Isotretinoin (N = 204)	Active control (N = 192)	Overall (N = 396)
Subjects with Bone Age change >1.5 SD and/or epiphysis closing	9/146 (6.2)	8/143 (5.6)	17/289 (5.9)
12-14 y/o	2/45 (4.4)	4/31 (12.9)	6/76 (7.9)
15-17 y/o	7/101 (6.9)	4/112 (3.6)	11/213 (5.2)
Patients with clinically significant findings after full evaluation	5/146 (3.4)	4/143 (2.8)	9/289 (3.1)
Bone age > 1.5 SD	2/146 (3.4)	1/143 (0.7)	3/289 (1.0)
Epiphysis Closing	0	0	0
Bone age > 1.5 SD and Epiphysis Closing	3/146 (2.1)	3/143 (2.1)	6/289 (2.0)

Source: Table 10-13, CSR App. 16.7

These 9 subjects with “clinically relevant” changes were relatively young (mean age 14.3 y/o) and were all males. The Sponsor concedes that they represent a group “for which a drug-related effect cannot be excluded”, but maintains that this number is “expected in a normal population”.

**Reviewer comment:** *It is unclear, without a placebo group, whether the small group of adolescents (almost all boys) who appear to show significant advance in bone age are outside the range of normal variation. The two isotretinoin products did not appear to differ in this respect. It is troubling that there is a highly significant difference between*

*the mean increase in chronologic age, and the mean increase in bone age, during the study.*

**Results - Adults (age 18 – 54 y/o)**

**Demographics – Adults**

Out of 529 adult (age 18-54 y/o) subjects in the overall study, 80 agreed to participate in the bone substudy and underwent baseline DXA scans. (The protocol stated that these would be conducted in 100 adults.) Demographics for these 80 subjects are given in **Table 13**; most (70%) were less than 30 years old. Unlike the adolescent subjects, there were somewhat more females than males, and the females were older (median age 28 y/o vs. 20 y/o). By chance, subjects assigned to the CIP-Isotretinoin arm had baseline T-scores that were significantly lower than the control subjects at all 3 skeletal sites, though there was only slight difference in median age, and the age ranges between the groups were similar.

**Table 13. Demographic and baseline characteristics – Adults**

	<b>CIP-Isotretinoin (N = 41)</b>	<b>Active control (N = 39)</b>	<b>Overall (N = 80)</b>
<b>Age (years)</b>			
Median	23	22	23
Range	18-49	18-41	18-49
<b>Gender</b>			
Male	44%	36%	40%
Female	56%	64%	60%
<b>Race</b>			
White	83%	87%	85%
Asian	15%	5%	8%
Other	2%	8%	5%
<b>Ethnicity</b>			
Hispanic	15%	10%	13%
Non-Hispanic	85%	90%	87%
<b>Hormonal contraceptive use*</b>	70%	52%	60%
<b>Weight – mean (kg)</b>	73.1	74.8	73.9
<b>25(OH) vitamin D (mean, in ng/mL)</b>	28.7	28.0	28.3
<b>L-spine T-score (mean)**</b>	-0.262	0.394	0.060
<b>Total hip T-score (mean)**</b>	-0.079	0.404	0.155
<b>Femoral neck T-score(mean)**</b>	-0.319	0.230	-0.054
* females only			
** p < .05 for CIP – control difference			
Source: Table 14.3.3.6.4, App. 16.7; ADBMD			

**DXA Results – Adults**

Among the 80 adults in the bone substudy, 30 of the 41 subjects assigned to CIP-Isotretinoin also had an EOT scan (73.2%), and 28 of the 39 subjects assigned to control also had an EOT scan (71.8%).

**Lumbar spine BMD** increased modestly in the adult subjects during the study, especially in the CIP-Isotretinoin arm. Mean BMD increases were similar between males (1.038%) and females (1.013%) T-scores (normalized to a gender-specific young-adult database) also increased slightly. (**Table 14**) No subject experienced a BMD decline from baseline greater than 3.3%.

**Table 14. Lumbar Spine BMD and T-score by treatment group – Adults (age 18-49 y/o)**

	<b>CIP-Isotretinoin</b> (N = 41)	<b>Active control</b> (N = 39)	<b>Overall</b> (N = 80)
<b>Baseline</b>			
N	41	39	80
BMD, Mean(SD) (g/cm <sup>2</sup> )	1.112 (0.151)	1.124 (0.172)	1.118 (0.161)
T-score, Mean (SD)	-0.262 (1.070)	0.394 (1.131)	0.060 (1.140)
p-value: T-score for CIP vs. control*	0.0259		
<b>Week 20</b>			
N	30	27	57
<b>Mean (SD) %Change in BMD from BL</b>	<b>1.561</b> (2.043)	<b>0.627</b> (2.101)	<b>1.119</b> (2.105)
p-value: CIP vs. control*	0.097		
Median	1.197	0.806	0.978
Range	-1.895, 5.993	-3.265, 5.257	-3.265, 5.993
# w/ increased BMD	24	17	41
# w/ decreased BMD	6	10	16
# w/ ≥ 7% decline	0	0	0
<b>Mean (SD) Change in T-score from BL</b>	<b>0.169</b> (0.207)	<b>0.123</b> (0.213)	<b>0.147</b> (0.208)
p-value: CIP vs. control*	0.4883		
*p-value from 2-sample paired t test Source: ADBMD			

**Total hip BMD**, and T-score, showed only slight changes during the study in the overall group of adults. (**Table 15**) However, the 27 adult males experienced a mean BMD decline (-0.454%), and the 41 adult females a mean BMD increase (0.387%) (p=0.05 for gender difference). The gender difference was also significant for change in total hip Z-score (-0.039 for males, 0.033 for females, p=0.0416) but not for T-score. No subject had a total hip BMD decline greater than 3.33%. Of the 8 subjects with BMD decline > 2% from baseline, 6 were male and 2 female. Unlike the adolescent females, the adult females who did not use oral contraceptives (n=17) had a better result than those who did (n=24) (mean BMD increases 0.831% and 0.072% respectively). The 47 adults younger than 30 y/o fared somewhat worse than the 21 older adults (mean BMD changes of -0.209% vs. 0.639%, p=0.06).

**Table 15 Total Hip BMD and T-score by treatment group – Adults (age 18-49 y/o)**

	CIP-Isotretinoin (N = 41)	Active control (N = 39)	Overall (N = 80)
<b>Baseline</b>			
N	41	39	80
BMD, Mean(SD) (g/cm <sup>2</sup> )	1.028 (0.142)	1.036 (0.124)	1.032 (0.132)
T-score, Mean (SD)	-0.079 (0.865)	0.404 (0.885)	0.155 (0.901)
p-value: T-score for CIP vs. control*	0.0369		
<b>Week 20</b>			
N	30	28	58
<b>Mean (SD) %Change in BMD from BL</b>	<b>-0.351</b> (1.424)	<b>0.330</b> (1.935)	<b>-0.022</b> (1.710)
p-value: CIP vs. control*	0.1308		
Median	-0.159	0.111	-0.045
Range	-3.333, 2.370	-3.176, 6.681	-3.333, 6.681
# w/ increased BMD	12	15	27
# w/ decreased BMD	18	13	31
# w/ ≥ 7% decline	0	0	0
<b>Mean (SD) Change in T-score from BL</b>	<b>-0.001</b> (0.101)	<b>0.066</b> (0.144)	<b>0.031</b> (0.127)
p-value: CIP vs. control*	0.0837		
*p-value from 2-sample paired t test			
Source: ADBMD			

**Femoral neck BMD**, and T-score, increased slightly in both adult treatment groups. (Table 16) In contrast to total hip BMD, results for males and females were similar (mean BMD change 0.557% and 0.394% respectively). Adult females not using oral contraceptives did slightly better than users (mean BMD increases of 0.594% and 0.252%). Similar to total hip, the younger adults ( $\leq 29$  y/o) did less well than those  $\geq 30$  y/o (mean BMD increases of 0.157% vs. 1.134%). There were 7 subjects (5 male and 2 female; 5 with CIP-Isotretinoin, 2 with control) who had BMD declines from -3.32% to -6.49%. None of these adult subjects underwent any additional follow-up scans, because none met the prespecified criterion of a BMD decline of  $\geq 7\%$  from baseline.

*Reviewer comment: Adult females had less favorable hip and femoral neck BMD results with OC use vs. non-use, an unexpected finding and counter to the trend in female adolescents. Because there were fewer adult females (n=48) compared to adolescent females (n=79), the trend in adolescents is perhaps more reliable, but the numbers in both groups may be too small to draw firm conclusions.*

**Table 16. Femoral Neck BMD and T-score by treatment group – Adults (age 18-49 y/o)**

	<b>CIP-Isotretinoin (N = 41)</b>	<b>Active control (N = 39)</b>	<b>Overall (N = 80)</b>
<b>Baseline</b>			
N	41	39	80
BMD, Mean(SD) (g/cm <sup>2</sup> )	0.965 (0.186)	0.976 (0.151)	0.970 (0.169)
T-score, Mean (SD)	-0.319 (1.043)	0.230 (0.921)	-0.054 (1.016)
p-value: T-score for CIP vs. control*	0.0355		
<b>Week 20</b>			
N	30	28	58
<b>Mean (SD) %Change in BMD from BL</b>	<b>0.251 (3.099)</b>	<b>0.979 (3.768)</b>	<b>0.602 (3.427)</b>
p-value: CIP vs. control*	0.4234		
Median	0.688	-0.076	0.571
Range	-6.488, 4.710	-4.4176, 16.064	-6.488, 16.064
# w/ increased BMD	21	13	34
# w/ decreased BMD	9	15	24
# w/ ≥ 7% decline	0	0	0
<b>Mean (SD) Change in T-score from BL</b>	<b>0.073 (0.211)</b>	<b>0.081 (0.322)</b>	<b>0.077 (0.268)</b>
p-value: CIP vs. control*	0.9270		
*p-value from 2-sample paired t test Source: ADBMD			

#### **Adverse Effects in Study ISOCT.08.01**

As noted in the label, previous Accutane studies appeared to show a higher incidence in adolescents, compared to adults, of back pain and arthralgias. It is not known whether there is any correlation between such symptoms and susceptibility to BMD effects and/or hyperostosis. In the current study, subjects were asked specific questions at each visit regarding any somatic pain symptoms. X-rays were not systematically performed in subjects experiencing such symptoms, therefore hyperostosis was not assessed.

Of the 27 subjects noted above as experiencing significant bone loss at one or more skeletal sites on DXA, there were 4 (#08024, #11004, #11025 and #37010) who reported back pain during the study. All of these were reported as “mild” and resolved before study end. The incidence of back pain within this group was consistent with the entire study population, about 20% of whom reported back pain. The only other musculoskeletal AEs in this group of 27 subjects were one with arthralgia/R knee pain (#08024) and joint sprain/sprained R ankle (#08036).

### **Summary/Conclusions**

A previous Accutane study in 217 adolescents (M01513) showed a significant mean increase from baseline (1.4%) in lumbar spine BMD, little change (-0.25%, p value was NS) in total hip BMD, and a significant decline (-0.5%, p= 0.03) in femoral neck BMD, over a typical 16-20 week course of treatment. Although the hip/femoral neck changes were small, they were considered to be of potential clinical concern because they ran counter to the expectation of BMD increases in this age group, and also because numerous subjects exhibited substantial BMD loss at lumbar spine ( $\geq 4\%$ ) or total hip ( $\geq 5\%$ ) during the study. Further, there was insufficient evidence of BMD recovery: eight of the subjects with substantial bone loss during treatment were re-tested 6-11 months later; three of the eight remained below baseline lumbar spine BMD, and five of the eight remained below baseline total hip BMD.

The current study, ISOCT.08.01, evaluates two other formulations of this drug (CIP-Isotretinoin and generic isotretinoin) over 20 weeks of treatment, with bone safety data in 396 adolescents (age 12-17 y/o) and 80 adults (18-49 y/o). In the adolescents, both treatment arms showed moderate increase (1.56% CIP-Isotretinoin, 2.04% generic isotretinoin control) in mean lumbar spine BMD, and little change in mean total hip BMD (-0.28%, 0.00%) or mean femoral neck BMD (-0.49% [NS], 0.05%). Small increases in BMC and bone area were consistent with the BMD changes at each skeletal site. Overall, BMD results from these adolescents were somewhat more favorable in the control arm relative to CIP-Isotretinoin at each skeletal site, but without statistical difference. These DXA findings are quite consistent with the previous study (M01513).

Mean Z-scores declined modestly (but significant statistically relative to baseline) at all 3 skeletal sites: -0.053 SD at lumbar spine, -0.109 at total hip, and -0.104 SD at femoral neck. These findings appear to indicate that these adolescents were not exhibiting the BMD increases typical of their peer groups during the study, particularly at the hip and femoral neck. In addition, Z-score declines at the hip and femoral neck were significantly greater in boys than in girls. In part, these gender differences may be because normal BMD accrual subsides in girls about 1-2 years before boys and also possibly because of oral contraceptive use by almost half of the girls, which may have had a protective effect.

Clinically significant bone loss in ISOCT.08.01 was also consistent with study M01513 in that approximately 9% of individual adolescent subjects (almost all males) exhibited potentially significant ( $> 4\text{-}5\%$ ) bone loss during the study, mostly at total hip and/or femoral neck. This finding is very unlikely to be an issue of DXA precision alone (as claimed by the Sponsor) because most of these subjects subsequently underwent a follow-up scan, which in every case confirmed a substantial decline in that subject's BMD. Normally, healthy adolescents experience rapid BMD increases. It cannot be ruled out that some normal adolescents may experience temporary declines in hip BMD, perhaps due to periods of rapid growth. However, this would be an unusual occurrence, as BMD Z-score has been shown to exhibit a high degree of "tracking" or within-patient consistency (comparable to that of height and weight Z-scores) over 3 years of growth in

adolescents of both genders (Kalkwarf 2010). Therefore, a more likely explanation of the study findings of potentially clinically significant bone loss is that isotretinoin therapy for acne has a negative effect on BMD in a subset (probably  $\leq 10\%$ ) of patients, particularly boys and perhaps younger more than in older adolescents. Though there were somewhat more CIP-Isotretinoin subjects with BMD decline in this study, compared to control, the difference between the CIP-Isotretinoin and generic isotretinoin treatment groups is probably not clinically significant.

The long-term clinical significance of BMD declines in individual adolescents, and significant declines in mean Z-scores across the overall adolescent study population, is unclear. The baseline fracture risk of adolescent populations is low, particularly in this study where mean Z-scores remained well above average even after treatment; even within the subset showing substantial BMD decline, most subjects continued to have “normal” Z-scores ( $>-1$ ). Most acne patients do not require a second course of isotretinoin, so a key question is how well the BMD recovers after the 20 weeks of treatment. Unfortunately the Sponsor did not agree under the terms of the SPA to conduct 1-year post-treatment BMD follow-up on adolescents with bone loss, and has no intent to do so, except in a single subject. The short-term follow-up DXA scans performed in this study (up to 4 months post-treatment) showed no evidence of a trend toward BMD recovery. A limited number of subjects underwent additional scans at 6-11 months post-treatment; although these appear to show improvement, about half of these subjects remained at or below their pre-treatment baseline (also consistent with study M01513). The data are inadequate to conclude that subjects with BMD loss related to isotretinoin will experience complete recovery from this effect; this BMD loss should be noted in the labeling.

In regard to bone age data, there was a highly significant difference of  $\sim 5$  months between the mean increase in chronologic age during the study, and the mean increase in bone age, for the overall adolescent population. There was a small group of adolescents who showed a significant advance in bone age, with no difference apparent between treatment groups. These subjects were similar to the group with excessive BMD decline in that they were somewhat younger on average than the overall adolescent population and were almost all male, however only 2 subjects met criteria for both BMD decline and bone age advance. The bone age findings do not allay the concerns about premature epiphyseal closure with isotretinoin previously raised by case reports and animal studies. However, a definitive answer on this issue (i.e. whether the drug has any effect on ultimate adult height) would require a placebo-controlled study of both CIP-isotretinoin and generic isotretinoin.

Adult BMD results in this study were similar to the adolescents in showing slight increases in mean lumbar spine BMD and minimal change in mean total hip or femoral neck BMD. Total hip BMD results were more favorable in women compared to men, bordering on statistical significance, however femoral neck data were similar between genders. Adults  $\geq 30$  y/o had more somewhat more favorable BMD results than younger adults. Unlike adolescent females, adult females who did not use oral contraceptives had slightly greater BMD increases than non-users. Several adults lost BMD at the femoral

neck up to 6.5% and had no follow-up studies, but this skeletal site has relatively less precision on DXA, and these adults were not expected to show major gains in BMD, unlike adolescents.

Overall, the study confirmed that there are bone safety concerns with CIP-Isotretinoin that are currently described in isotretinoin labeling. In both adolescents and young adults, the study did not demonstrate any significant differences in effect on bone between CIP-Isotretinoin and generic isotretinoin.

### **Recommendations for labeling**

The PI for the reference listed drug for this 505(b)(2) application, Accutane, is in pre-PLR format. Because the bone-related findings of study ISOCT.08.01 are consistent with previous studies, no changes to these sections of the approved Accutane or isotretinoin product labels are warranted. Following are the bone-related subsections of: (1) current approved Accutane labeling; (2) the Sponsor's proposed PI for the new CIPHER product, with proposed trade name (b) (4); and (3) Sponsor's proposal with edits recommended by DRUP:

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### **Current Accutane labeling**

#### **WARNINGS**

##### **Skeletal**

##### **Bone Mineral Density**

Effects of multiple courses of Accutane on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a

decrease in mean lumbar spine bone mineral density up to 3.25% (see **PRECAUTIONS: Pediatric Use**).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the Accutane population. While causality to Accutane has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Accutane be given at the recommended doses for no longer than the recommended duration.

#### Hyperostosis

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization<sup>6</sup> Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Accutane treatment courses for acne are unknown.

In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of Accutane given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

#### Premature Epiphyseal Closure

There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Accutane. The effect of multiple courses of Accutane on epiphyseal closure is unknown.

## **PRECAUTIONS**

### **General**

Although an effect of Accutane on bone loss is not established, physicians should use caution when prescribing Accutane to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on therapy with Accutane or following cessation of therapy with Accutane while involved in these activities. While causality to Accutane has not been established, an effect must not be ruled out.

### **Pediatric Use**

The use of Accutane in pediatric patients less than 12 years of age has not been studied. The use of Accutane for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see **PRECAUTIONS: General**). Use of Accutane in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients ( $\geq 18$  years). Results from this study demonstrated that Accutane, at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

In studies with Accutane, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see **ADVERSE REACTIONS**).

In an open-label clinical trial (N=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change  $> -4\%$  and total hip change  $> -5\%$ ) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density  $> 4\%$  based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density  $> 4\%$ , and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density  $> 5\%$  based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density  $> 5\%$ , and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range  $-1.6\%$  to  $-7.6\%$ ) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13 to 18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see **WARNINGS: Skeletal: Bone Mineral Density**).

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**Sponsor proposed labeling**



(b) (4)

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/s/  
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STEPHEN R VOSS  
04/10/2012

THERESA E KEHOE  
04/10/2012

AUDREY L GASSMAN  
04/10/2012

Medical Officer's Review of NDA 21-951  
Request for Ophthalmology Consultation – Review #2

NDA 21-951

**Submission Date:** 11/29/11  
**Consultation Date:** 12/20/11  
**Review Date:** 3/28/12

**Applicant:**

Cipher Pharmaceuticals, Inc  
5650 Tomken Road, Unit 16  
Mississauga  
Ontario L4W 4P1  
Canada

**Drug:**

Cip-Isotretinoin capsules

**Proposed Indication:**

Severe recalcitrant nodular acne

**Background:**

In a submission dated Friday, March 23, 2012, Cipher Pharmaceuticals, Inc submitted a response to the Agency's information request dated February 17, 2012, and email information request dated March 30, 2012.

**1. The analyses provided in the Clinical Study Report (CSR) relating to visual acuity and adverse events (ocular) are not correctly performed.**

**a. Visual acuity assessed on the Snellen Eye Chart is reported as a "line shift" away/towards 20/20. This is incorrect because 20/20 is not the best vision that can be achieved. Some line shifts from 20/20 represent improvement in visual acuity and some line shifts represent an impairment of visual acuity. It is important to count improvement in visual acuity as an improvement and distinguish it from a worsening of vision.**

**Snellen Visual acuity is best analyzed by conversion to logMAR, then reporting -0.3, - 0.2, -0.1, 0, 0.1, 0.2, 0.3 and >0.3 log changes. The Snellen acuity for each subject on each visit is recorded so it should be converted and analyzed.**

Appendix 2: Summary of Ophthalmic Assessment, Snellen Chart LogMar Change from Baseline Safety Population provides reporting -0.3, -0.2, -0.1, 0, 0.1, 0.2, 0.3 and >0.3 log changes from Baseline after logMAR conversion for all observed patients in the Safety population by study visit.

**Summary of Ophthalmic Assessment, Snellen Chart  
LogMar Change from Baseline  
Safety Population**

Cipher Pharmaceuticals Inc.  
Protocol No : ISOCT.08.01

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**Table 1A. Summary of Ophthalmic Assessment, Snellen Chart  
LogMar Change from Baseline  
Safety Population**

	TEST		Reference	
	Left Eye	Right Eye	Left Eye	Right Eye
<b>Week 4</b>				
N	444	444	450	450
< -0.3	7 (1.6)	4 (0.9)	4 (0.9)	5 (1.1)
-0.3	6 (1.4)	2 (0.5)	5 (1.1)	6 (1.3)
-0.2	24 (5.4)	27 (6.1)	19 (4.2)	19 (4.2)
-0.1	64 (14.4)	63 (14.2)	64 (14.2)	57 (12.7)
0	297 (66.9)	300 (67.6)	309 (68.7)	311 (69.1)
0.1	27 (6.1)	36 (8.1)	33 (7.3)	35 (7.8)
0.2	13 (2.9)	10 (2.3)	6 (1.3)	10 (2.2)
0.3	5 (1.1)	1 (0.2)	7 (1.6)	1 (0.2)
> 0.3	1 (0.2)	1 (0.2)	3 (0.7)	6 (1.3)
<b>Week 8</b>				
N	438	438	436	436
< -0.3	6 (1.4)	1 (0.2)	6 (1.4)	8 (1.8)
-0.3	6 (1.4)	5 (1.1)	9 (2.1)	7 (1.6)
-0.2	22 (5.0)	28 (6.4)	28 (6.4)	24 (5.5)
-0.1	77 (17.6)	63 (14.4)	71 (16.3)	58 (13.3)
0	275 (62.8)	288 (65.8)	269 (61.7)	286 (65.6)
0.1	34 (7.8)	39 (8.9)	35 (8.0)	37 (8.5)
0.2	11 (2.5)	8 (1.8)	7 (1.6)	9 (2.1)
0.3	5 (1.1)	4 (0.9)	7 (1.6)	3 (0.7)
> 0.3	2 (0.5)	2 (0.5)	4 (0.9)	4 (0.9)
<b>Week 12</b>				
N	425	425	427	427
< -0.3	9 (2.1)	3 (0.7)	5 (1.2)	6 (1.4)
-0.3	10 (2.4)	11 (2.6)	7 (1.6)	7 (1.6)
-0.2	25 (5.9)	30 (7.1)	31 (7.3)	34 (8.0)
-0.1	85 (20.0)	83 (19.5)	75 (17.6)	72 (16.9)
0	245 (57.6)	241 (56.7)	259 (60.7)	257 (60.2)
0.1	33 (7.8)	43 (10.1)	34 (8.0)	39 (9.1)
0.2	10 (2.4)	8 (1.9)	11 (2.6)	6 (1.4)
0.3	5 (1.2)	4 (0.9)	3 (0.7)	6 (1.4)
> 0.3	3 (0.7)	2 (0.5)	2 (0.5)	0

Note: Change from Baseline is calculated as the post-Baseline value minus the Baseline value.

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**Summary of Ophthalmic Assessment, Snellen Chart  
LogMar Change from Baseline  
Safety Population**

Cipher Pharmaceuticals Inc.  
Protocol No : ISOCT.08.01

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**Summary of Ophthalmic Assessment, Snellen Chart  
LogMar Change from Baseline  
Safety Population**

	TEST		Reference	
	Left Eye	Right Eye	Left Eye	Right Eye
<b>Week 16</b>				
N	415	415	416	416
< -0.3	8 (1.9)	4 (1.0)	6 (1.4)	5 (1.2)
-0.3	7 (1.7)	10 (2.4)	9 (2.2)	11 (2.6)
-0.2	32 (7.7)	43 (10.4)	33 (7.9)	30 (7.2)
-0.1	77 (18.6)	71 (17.1)	80 (19.2)	73 (17.5)
0	232 (55.9)	233 (56.1)	240 (57.7)	245 (58.9)
0.1	38 (9.2)	36 (8.7)	34 (8.2)	37 (8.9)
0.2	15 (3.6)	11 (2.7)	10 (2.4)	13 (3.1)
0.3	4 (1.0)	3 (0.7)	3 (0.7)	0
> 0.3	2 (0.5)	4 (1.0)	1 (0.2)	2 (0.5)
<b>Week 20</b>				
N	404	404	407	407
< -0.3	9 (2.2)	5 (1.2)	4 (1.0)	6 (1.5)
-0.3	8 (2.0)	8 (2.0)	12 (2.9)	13 (3.2)
-0.2	29 (7.2)	33 (8.2)	31 (7.6)	29 (7.1)
-0.1	86 (21.3)	79 (19.6)	91 (22.4)	75 (18.4)
0	216 (53.5)	222 (55.0)	226 (55.5)	228 (56.0)
0.1	40 (9.9)	40 (9.9)	29 (7.1)	41 (10.1)
0.2	9 (2.2)	9 (2.2)	10 (2.5)	8 (2.0)
0.3	7 (1.7)	6 (1.5)	3 (0.7)	5 (1.2)
> 0.3	0	2 (0.5)	1 (0.2)	2 (0.5)
<b>Week 24</b>				
N	399	399	405	405
< -0.3	4 (1.0)	5 (1.3)	9 (2.2)	10 (2.5)
-0.3	7 (1.8)	7 (1.8)	10 (2.5)	10 (2.5)
-0.2	37 (9.3)	40 (10.0)	29 (7.2)	32 (7.9)
-0.1	88 (22.1)	71 (17.8)	95 (23.5)	77 (19.0)
0	206 (51.6)	223 (55.9)	212 (52.3)	231 (57.0)
0.1	38 (9.5)	34 (8.5)	33 (8.1)	28 (6.9)
0.2	11 (2.8)	10 (2.5)	12 (3.0)	11 (2.7)
0.3	3 (0.8)	3 (0.8)	1 (0.2)	4 (1.0)
> 0.3	5 (1.3)	6 (1.5)	4 (1.0)	2 (0.5)

Note: Change from Baseline is calculated as the post-Baseline value minus the Baseline value.

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**Reviewer's Comments:**

*There are no significant between group differences.*

**b. When data listings are reviewed, there are numerous instances where decreased vision under dim light condition is coded as "visual acuity reduced." This**

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**inaccurately captures the number of reported cases of both visual acuity reduction and night blindness. In addition, as an adverse event, it is not clear how Xerophthalmia is being distinguished from Dry Eye or how conjunctival hyperemia is being distinguished from conjunctivitis. The incidence of eye events should be recalculated.**

The FDA is correct, there were five AEs in which the verbatim description includes “decreased vision under dim light” which were coded by coding personnel as “visual acuity reduced” (Patients: 01/003; 03/002, 31/008, 39/007, 39/010).

Cipher Pharmaceuticals has provided recalculated tables in response to the question, by classifying these five (5) patients under “night blindness” (see Table 1 and Table 2).

**Table 1: Number and Percentage of Patients, Safety Population:**

Preferred Term	Original Coding		Alternative Coding	
	TEST (N=464)	Reference (N=460)	TEST* (N=464)	Reference** (N=460)
Night blindness	6 (1.3)	3 (0.7)	10 (2.2)	4 (0.9)
Visual acuity reduced	23 (5.0)	25 (5.4)	20 (4.3)	25 (5.4)
*Patient 31/008 (TEST) had another AE of decreased vision to right eye which was coded visual acuity reduced, so this patient is counted in both places under the recoding.				
**Patient 01/003 (Reference) had another AE of decreased visual acuity which was coded visual acuity reduced, so this patient is counted in both places under the recoding.				

**Reviewer’s Comments:**

*10/464 or 2% of test product subjects were reported as having night blindness. 4/460 or 1% of reference drug subjects were reported as having night blindness.*

*20/464 or 4% of test product subjects were reported as having reduced visual acuity. 25/460 or 5% of reference drug subjects were reported as having reduced visual acuity.*

**Table 2: Full Summary of Adverse Events “Eye Disorders” Recalculated:**

Cipher Pharmaceuticals Inc.  
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Table 14.3.1.3: Summary of Adverse Events by System Organ Class and Preferred Term Safety Population

	TEST (N=464)	Reference (N=460)
Patients with Any AE, n (%)	144 (31.0)	135 (29.3)
<b>Eye disorders</b>	139 (30.0)	126 (27.4)
Dry Eye	90 (19.4)	80 (17.4)
Visual acuity reduced	20 (4.3)	25 (5.4)
Vision blurred	14 (3.0)	15 (3.3)
Eye pruritus	9 (1.9)	17 (3.7)
Night blindness	10 (2.2)	4 (0.9)
Eye irritation	5 (1.1)	5 (1.1)
Asthenopia	5 (1.1)	4 (0.9)
Ocular hyperaemia	4 (0.9)	5 (1.1)
Conjunctivitis	6 (1.3)	2 (0.4)
Lacrimation increased	2 (0.4)	5 (1.1)
Photophobia	4 (0.9)	1 (0.2)
Blepharitis	1 (0.2)	2 (0.4)
Eye pain	2 (0.4)	0
Visual impairment	1 (0.2)	1 (0.2)

Note: Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the MedDRA system organ class / preferred term. A patient may be counted once only in each row of the table.

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### **Reviewer’s Comments:**

*See previous comments for Table 1.*

*Note that roughly 20 % of subjects in each group were reported as having dry eye.*

**c. The protocol states that patients who present with issues requiring a full ophthalmic work-up will be referred to the patient’s own or a local ophthalmologist recommended by the investigator for further evaluation. Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the night blindness.**

**Two subjects in the CIP-isotretinoin group discontinued due to eye events (night blindness; punctate keratitis), but there is no discussion or analysis within the study report indication the number of subjects requiring a full ophthalmic workup or what was found during the full ophthalmic workup. This information should be provided. If only two subjects were referred for full evaluation, there should be an**

**explanation why patients were referred for evaluation, but the evaluation was not analyzed.**

**The CSR states that follow-up reports of available [ophthalmic] evaluations were included in the patient's study record. This information does not appear to be present in Appendix 16.3.1 for subjects 23/004 and 43/002. The exact location of the follow-up reports of available ophthalmic evaluations for these subjects should be provided.**

Cipher Pharmaceuticals notes that the CSR was not specific, and could have been more specific. These data are located in patient specific files located at the respective sites.

With respect to "Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the "night blindness." Based on the FDA commentary, the protocol was re-reviewed, and investigators queried. Given that these investigators have extensive experience with isotretinoin and are all well versed in the adverse events thereof, the term "night blindness" was generally interpreted as a severe change in night vision acuity. Hence, it was the investigator's interpretation of night blindness and severity that elucidated a request for ERG. Minor changes were noted and coded through MedDRA as night blindness.

**Reviewer's Comments:**

*Per the ISOCT.08.01 protocol dated February 3, 2010, Version 4.0:*

*Patients who present with issues requiring a full ophthalmic work-up will be referred to the patients own or a local ophthalmologist recommended by the investigator for further evaluation. Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the night blindness. Follow-up reports of the ophthalmic evaluations available at the time will be included in the patient's study records.*

*Investigators do not appear to have followed the protocol based on Cipher's response above from March 30, 2012.*

*The submitted narratives were reviewed.*

**Table 3: Ophthalmic Narrative Summary**

<b>Patient</b>	<b>Description in Narrative</b>	<b>Ophthalmic Referral</b>	<b>Resolved</b>
01/003	Decreased vision more than usual under dim light conditions.	Yes, patient did not go.	Yes
03/002	Decreased vision under dim lighting conditions	Yes: ERG within Normal Limits	Yes
08/016	Decreased vision at night	No	Yes
13/016	Decreased vision in dark right eye only	No	Unknown, Pt. ET related to abdominal pain and was LTF

<b>Patient</b>	<b>Description in Narrative</b>	<b>Ophthalmic Referral</b>	<b>Resolved</b>
23/004	Superficial Punctate Keratopathy (SPK) SPK defined by Ophthalmologist	Yes: recommendation was made to DC patient.	Yes
25/002	Decreased vision at night	No	Yes
28/029	Decreased night vision	No	Yes
30/006	Worse dim light vision at night	No	Yes
31/008	Decreased vision under dim light conditions	No	Yes
35/022	Decreased vision at night	No: resolved during treatment	Yes
39/007	Decreased vision under dim light conditions	Yes: Report not received	Yes
39/010	Decreased vision under dim light conditions	Yes, within normal limits	Unknown, Pt. ET and was LTF
39/012	Decreased vision at night	Yes, ERG within Normal Limits	Yes
40/001	Decreased Night Vision	No: resolved during treatment	Yes
43/002	Decreased night vision	Yes, ERG within Normal Limits	Yes

**Reviewer's Comments:**

*Based on reviewed narratives and Table 3 provided in the March 30, 2012, submission, protocol mandated referral to an ophthalmologist and request for ERG was arbitrary and inconsistent.*

**Summary Statement/ Recommended Action:**

## Summary Statements:

- 1) As designed and conducted, this protocol did not provide adequate ocular monitoring of study subjects; the ocular safety of the study treatments were not adequately addressed. To evaluate ocular safety, the protocol would have needed to include assessments of the conjunctiva, cornea, lens, optic nerve, retina, color vision, dark adaptation, retinal electrical activity, and tear production.

The potential adverse reactions from clinical studies and post-marketing experience of marketed isotretinoin cited in Section 8.1 of the protocol related to vision (e.g. corneal opacities, decreased night vision, cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, and visual disturbances) were not adequately assessed in study subjects.

Although flawed, there are no safety signals identified in ISOCT.08.01 which indicate that Cipher Pharmaceuticals' cip-isotretinoin capsules should not share ocular labeling consistent with the reference drug product.

- 2) The analyses provided in the Clinical Study Report (CSR) relating to visual acuity and adverse events (ocular) were not correctly performed originally. The revised acuity and adverse event data do not alter the conclusions of Summary Statement item 1 listed above.

## Recommendations:

Because this protocol did not provide adequate ocular monitoring of study subjects, the ocular safety of the study treatments were not adequately addressed. It is recommended that specific reference to the ophthalmologic findings of this clinical trial (ISOCT.08.01) be eliminated from the proposed labeling for the drug product.

The general statements regarding isotretinoin products found in Section 5.13 and throughout the package insert and patient package insert should be retained. DTOP will continue to work with the Division of Dermatology and Dental Drug Products on the product labeling for cip-isotretinoin capsules and will attend the scheduled labeling meetings.

Draft labeling is attached at the end of this review. It is understood that the Medication Guide may not be currently altered; the suggested revisions are for future consideration.

William M. Boyd, M.D.  
Clinical Team Leader

17 Pages of Draft Labeling have been Withheld in Full a B4  
(CCI/TS) Immediately Following this Page

NDA 21-951 Cip-isotretinoin capsules  
DTOP Review #2

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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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WILLIAM M BOYD  
04/02/2012

WILEY A CHAMBERS  
04/09/2012

## Center for Devices and Radiological Health

(ODE/DOED/ENTB)

### Audiology Review

**To:** Matthew White, Regulatory Project Manager  
Division of Dermatology and Dental Products (CDER)

**From:** James K. Kane, Ph.D.

**Thru:** Srinivas Nandkumar, Ph.D. *S.N. 2/28/2012*  
Chief, ENT Branch

**Date:** February 28, 2012

**Re:** NDA 21951 (Cipher Pharmaceuticals, Inc.)

I have reviewed this submission and present the following summary and evaluation:

#### **I. Background**

The current study was conducted to evaluate the safety and efficacy of a new formulation of isotretinoin. CIP-ISOTRETINOIN has been developed as a new formulation for which absorption is less dependent on the amount and/or type of food intake, thus providing a more reliable isotretinoin blood concentration.

Previously (July 4, 2008) the sponsor submitted a Phase 3 protocol for Special Protocol Assessment (SPA) which included an audiological safety assessment plan. That submission (IND 64,927, Serial# 014) was reviewed (dated July 31, 2008) and six audiological deficiencies were identified. Subsequently (February 10, 2009), the sponsor submitted a revised protocol for SPA (IND 64,927, Serial# 024). Review of that protocol (March 10, 2009) showed that the six previously identified audiological deficiencies still remained outstanding. Nevertheless, CDER/DDDP arrived at agreement with the sponsor regarding audiology assessments without consulting the ENT Branch (CDRH). That is, a DDDP clinical review dated 11/12/08 outlines agreements between the DDDP and the sponsor regarding audiology assessments. The agreements were communicated to the sponsor in a teleconference. The review is available at <http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/029bc1>.

Also, a Special Protocol Assessment (SPA) review dated 4/14/09 includes the agreed upon audiology assessments and what the sponsor should add to the protocol, according

NDA 21951  
Cipher Pharmaceuticals, Inc.

to DDDP. The review includes when the comments were conveyed and when agreements were reached. The review is available at <http://erom.fda.gov/eRoom/CDER3/CDERDivisionofDermatologyandDentalProducts/029bc2>.

Relevant content from the DPPP Medical Officer's review (04/14/09, P.15) is copied below:

**Reviewer's comment:**

- *Regarding the auditory assessment, agreements were reached on the following:*
    - *The audiometric testing will be conducted at an audiology clinic or within the dermatology clinic in a quiet examining room free from distracting outside noise.*
    - *Equipment used by the participating audiology clinics will be calibrated at least once annually according to the Standard Operating Procedures of the clinic. Audiometers and headphones used within the dermatology clinic will be supplied by (b) (4). Each participating site will receive the equipment (Amplitude TD Series handheld unit and headphones) calibrated together along with an Audiometer Calibration Certificate providing the following information: model, serial number, S/N Left, S/N Right, Mic./Sensor Description, Coupler Description, S/N, Mic Cal Date, Type, and Calibration Information with Reference Standards.*
    - *The audiometers used in general audiology clinics and those that will be supplied by (b) (4) are type 3 or type 4 devices that are approved by The American National Standards Institute for the purposes of audiology screening. These devices have a range of 250D8000Hz. If a significant threshold shift occurs as defined in the protocol the subject will be referred to a hearing specialist for follow up which, according to the clinical judgment of the specialist, may include additional tests such as (b) (4) emission assessment.*
    - *Within the participating dermatology sites, research nurses and coordinators will be trained by trainers experienced in providing training on (b) (4) Amplitude-T series equipment. Automatic and manual modes of operation will be taught. Research staff will be tested on their ability to conduct screening audiograms on a minimum of two volunteers in addition to a self test, in the presence of the trainer.*
    - *Within the audiology clinics the audiology assessments will be conducted by the audiologists on staff. The audiologists will be trained by sponsor representatives or the research site staff on protocol specific audiology procedures.*
- (Submission 10/07/08)*  
*However, all details are not found in the current proposed protocol.*
- *T-con 03/23/09: The sponsor is advised that the protocol should be revised to include above information).*
  - *The sponsor has agreed (Submission dated 03/24/09, SN 028)*

The current Phase III study was conducted based on the audiology agreements noted above between DDDP and the sponsor.

## **II. Study Title / Protocol / Overview**

**A Double-Blind, Randomized, Phase III, Parallel Group Study Evaluating the Efficacy and Safety of CIP- ISOTRETINOIN in Patients with Severe Recalcitrant Nodular Acne / Protocol # ISOCT.08:01**

This study was a multicenter, double-blind, randomized, parallel-group, noninferiority study that compared the safety and efficacy of CIP-ISOTRETINOIN with a Reference Product in retinoid-naïve patients aged 12-54 years with severe recalcitrant nodular acne (10 or more facial and/or truncal nodular lesions). Eligible patients underwent 20 weeks of treatment, including 4 weeks titration with 0.5 mg/kg/day divided into 2 doses taken with meals and 16 weeks at a stable dose of approximately 1 mg/kg/day divided into 2 doses taken with meals, followed by a 4-week post-treatment follow-up phase.

A generic isotretinoin was chosen as the reference product because the marketing of Accutane® in the US was discontinued in June 2009 and consequently it was not available in sufficient quantities to be used as a comparator in this study.

## **III. Research Objective**

The objectives of the study were to:

- Compare the efficacy and safety of CIP-ISOTRETINOIN and a marketed (generic) formulation of isotretinoin (Reference Product) when both are administered twice daily with meals; and
- Evaluate the safety profile of CIP-ISOTRETINOIN.

## **IV. Study Period**

The study has a 20-week treatment phase and a 4-week follow-up phase. Study period was from 23 September 2009 to 20 April 2011.

## **V. Study Sites / Population**

Thirty-eight (38) sites in the United States and 11 sites in Canada participated in the study (one additional Canadian site did not enroll any patients).

Planned = 800 completing patients. Screened = 1265. Randomized = 925. Completed = 795. Intent-to-Treat (ITT) Population = 925. Per Protocol (PP) Population = 724.

Of the 1265 patients screened for the study, a total of 925 were randomized for study inclusion and 340 were considered to be screen failures. Of the 925 patients who were randomized, a total of 813 (87.9%) patients completed the treatment phase of the study and 795 (85.9%) patients completed the follow-up phase.

Overall 130 (14.1%) patients discontinued from the study, 70 (15.1%) from the CIP-ISOTRETINOIN group and 60 (13.0%) from the Reference Product group. In both treatment groups, the most frequent reason for discontinuation was that the patient was lost to follow-up: 20 (4.3%) patient in the CIP-ISOTRETINOIN group and 16 (3.5%) patients in the Reference Product group. In addition, 34 (3.7%) patients discontinued due to one or more AEs, 19 (4.1%) in the CIP-ISOTRETINOIN group and 15 (3.3%) in the Reference Product group. Thirty (3.2%) patients, 15 in each group (3.2% in the CIP-ISOTRETINOIN group and 3.3% in the Reference Product group), withdrew their consent.

## **VI. Experimental Design**

This was a double-blind, randomized, Phase III, active-control, parallel-group, multicenter study that evaluated the safety and efficacy of CIP-ISOTRETINOIN in patients with severe recalcitrant nodular acne. This study consisted of a 20-week treatment phase and a 4-week follow-up phase in which patients were scheduled for a total of 9 visits (1 screening visit and 8 on-study visits). Patients determined to be eligible during the screening phase were randomized to 2 treatment groups, CIP-ISOTRETINOIN and Reference Product, in a 1:1 ratio stratified by gender and study site. Study medication was taken at an initial titration dose of approximately 0.5 mg/kg/day divided into 2 doses taken with meals for the first 4 weeks, followed by approximately 1 mg/kg/day divided into 2 doses taken with meals for 16 weeks. The duration of each patient's study participation was approximately 24 weeks, excluding a screening period of duration up to 45 days or more for certain females and patients who required Vitamin D supplementation.

The sample size was estimated from previous studies described in the literature and the relative responses described. Based on previous reports, the proportion of patients in whom a 90% reduction in total nodular lesion count was observed from Baseline to Week 20 of isotretinoin treatment was estimated to be approximately 70% of the patient population. The mean reduction in lesion count was estimated to be 17. Using these values for the true population statistics, simulations show that the sample size of 400 patients per treatment group yields more than 85% power for the planned noninferiority test procedures for the coprimary efficacy endpoints as described in Section 9.7.1.4.

The study was not sized to permit statistical comparisons of the two treatment groups with respect to safety outcomes. However, for events observed with incidence of less than 10%, the half-width of the 95% 2-sided CI of the absolute risk for the treatment was less than 3% with this sample size.

The study design is depicted schematically in Table 9-1.

## **VII. Inclusion Criteria**

See Section 9.3.1 (Page 46)

## **VIII. Exclusion Criteria**

See Section 9.3.2 (Page 18)

## **IX. Safety Data**

**Safety Population:** All randomized patients who consumed at least one dose of study medication, including those for whom dosing information was unknown. All safety analyses were performed using the Safety population, based on the actual treatment received.

All safety variables were analyzed using the safety population. Adverse events were summarized by frequency and system organ class and preferred term as follows: overall, treatment-related, and overall and treatment-related by maximum severity, by gender, and by age group (12-17 years,  $\geq 18$  years). In addition, serious AEs and AEs resulting in discontinuation were summarized by frequency.

Descriptive statistics for Baseline and change from Baseline at each visit were determined for the PHQ-8, the GAD-7, BMD and Z-score determinations, and Bone Age assessments. Bone Mineral Density and Z-score data were compared between treatment groups using the t test.

The proportion of patients with significant findings was determined and a 95% CI of the difference in the two proportions was calculated using Newcombe's Preferred Method for the following variables:

- Total score  $\geq 10$  on the PHQ-8 or the GAD-7, a suicidal episode on the C-SSRS, or a psychotic episode;
- Bone loss as measured by the BMD (adult patients) or Z-score (pediatric patients);
- Bone age outside the normal range (in pediatric patients);
- Newly emergent musculoskeletal symptoms;
- Confirmed audiology shifts;
- Worsening of visual acuity.

Frequency tables were constructed for the shift from Baseline to the Week 20 visit in Tanner Stage, response to individual questions on the Musculoskeletal survey.

### **Safety Results - General:**

The two treatment groups were similar with respect to all parameters of treatment exposure. The number of actual dosing days in the Safety population ranged from 1 to

174 days (mean = 130.7 days). Overall, 834/924 patients (90.3%) of the Safety population received treatment for at least 16 weeks, and 807/924 patients (87.3%) received at least 19 weeks of treatment. Excluding missing data from the analysis, 837/924 patients (90.6%) of the overall Safety population received between 0.375 and 0.625 mg/kg/day (75% to 125% of the prescribed dose) during the first 4 weeks, and 735/924 patients (79.5%) received between 0.75 and 1.25 mg/kg/day during the remaining 16 weeks of the study. The average daily dose was 0.5 mg/kg/day during the first 4 weeks and 0.9 mg/kg/day in Weeks 5 through 20.

Adverse events, most of which were considered to be treatment related, were reported in approximately 90% of the patients in both treatment groups. The most frequently reported AEs were those in the following body systems: the oral cavity (contained within the gastrointestinal System Organ Class [SOC]); skin and subcutaneous tissue; musculoskeletal system and connective tissue; infections and infestations; the eye; and respiratory system/thoracic and mediastinal areas. The incidence and types of AEs were similar between the two treatment groups. There was no statistically significant difference between the treatment groups in the overall AE incidence or in the incidence of those AEs considered to be of greatest clinical significance, i.e., those classified as psychiatric, vascular, or cardiac events or events related to the eye, ear and labyrinth, musculoskeletal system and connective tissue, or gastrointestinal system.

#### **Safety: Ear and Labyrinth Events – Safety Population**

Adverse events classified as ear and labyrinth events are summarized in Table 12-11 and Post-text Table 14.3.1.3. A by-patient listing of ear and labyrinth events is provided in Data Listing 16.2.7.6.

**Table 12-11 Ear and Labyrinth Events-Safety Population**

	CIP- ISOTRETINOIN (N = 464)	Reference Product (N = 460)
Patients with Any Ear or Labyrinth Events, n (%)	10 (2.2)	10 (2.2)
Ear pain	3 (0.6)	3 (0.7)
Hypoacusis	3 (0.6)	2 (0.4)
Ear discomfort	0	3 (0.7)
External ear inflammation	1 (0.2)	1 (0.2)
Cerumen impaction	0	1 (0.2)
Ear deformity acquired	1 (0.2)	0
Hyperacusis	0	1 (0.2)
Tinnitus	1 (0.2)	0

Vertigo

1 (0.2)

0

Source: Post-text Table 14.3.1.3.

Note: Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the MedDRA system organ class / preferred term. A patient may be counted once only in each row of the table.

Adverse events classified as ear and labyrinth events were reported in 20 patients overall: 10 (2.2%) patients in the CIP-ISOTRETINOIN group and 10 (2.2%) patients in the Reference Product group.

Adverse events related to the ear and labyrinth were reported in approximately 2 percent of the patients in each treatment group, and only a small number of patients reported a threshold shift during an audiology test.

#### Audiology Assessments (Section 12.7, p. 174)

Audiology threshold shifts from Baseline to End of Treatment are summarized overall and by age group in Table 12-21 and Post-text Table 14.3.4.1. Audiology assessments for individual patients are presented in Data Listing 16.2.9.8.1 and audiology assessments for patients with a confirmed threshold shift are presented in Data Listing 16.2.9.8.2.

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Table 14.3.4.1: Summary of Audiology Assessment  
Patients with Audiology Test  
Safety Population

	TEST (N = 86)	Reference (N = 94)
<b>Patients with a Threshold Shift in Either Ear at End of Treatment</b>	<b>2186 (2.3)</b>	<b>5194 (5.3)</b>
Proportion Difference	-2.99	
95% Confidence Interval <sup>a</sup>	-9.74, 3.52	
<b>By Age Group</b>		
12-14 years	1110 (10.0)	1111 (9.1)
15-17 years	0722 (0.0)	2130 (5.6)
>= 18 years	1154 (1.9)	2147 (4.3)
< 18 years (All Pediatric Patients)	1132 (3.1)	3147 (6.4)

<sup>a</sup> Patients with evaluations at both Screening and Week 20 (End of Treatment)

<sup>b</sup> 95% confidence interval on difference in proportions (TEST minus Reference) using Newcombe's Preferred Method.

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A total of 180 patients in the study underwent audiology testing; 86 patients in the CIP-ISOTRETINOIN group and 94 patients in the Reference Product group. Two (2.3%)

patients in the CIP-ISOTRETINOIN group and 5 (5.3%) patients in the Reference Product group experienced a threshold shift in either ear. As indicated by the 95% CI (-9.74, 3.52), the difference between the treatment groups was not statistically significant.

Reviewer Comment: The 86 subjects in the CIP-ISOTRETINOIN group represent 18.5% (86/464=18.5%) of the experimental group subjects; likewise, the 94 subjects in the Reference Product group represent 20.4% of this control group (94/460=20.4%). Thus, hearing safety decisions related to the experimental drug are based on a small percentage (180/924=19.4%) of the total subjects participating in this study. CDER will need to decide if these small subgroups are sufficient for safety decisions / labeling.

The number of sites and the number of subjects per site for the experimental and control group subjects who had auditory assessments in this study could not be determined from the documents reviewed. Thus, it remains unknown if these subgroups represent 25% of the clinical sites as specified in the sponsor's protocol.

Data Listing 16.2.9.8.2 reported seven subjects who had confirmed threshold shifts. Review of these data showed that the greatest magnitude thresholds shifts occurred at 8000 Hz for six of the subjects; two subjects had thresholds shifts at 6000 Hz, and one subject had threshold shifts at 1000-, 2000-, and 4000 Hz.

## **X. Reviewer Comment**

The prior audiological deficiencies and the agreed upon audiological assessment content between the sponsor and DDDP are reviewed individually below:

**Def.#1.** You have not provided a rationale for monitoring only a subset of subjects (subjects at 25% of the clinical sites) for potential ototoxicity effects in this study. The number of subjects seen at each site may range from a minimum of eight to a maximum of 40; thus, the assessment of the potential effect of the drug on auditory sensitivity in experimental subjects may range from a minimum sample of 96 subjects (96/700 = 14%) to a maximum sample of 320 subjects (320/700 = 46%) of the total subject population completing the study (n=700). Because the comparator drug, Accutane®, is known to have caused permanent hearing loss, as well as tinnitus, all subjects in this study receiving the experimental drug should be monitored for this significant safety concern, not just a subset of subjects. Please modify your protocol to evaluate all subjects for potential ototoxic drug effects or provide your rationale for not doing so. In addition, you should report the rate of occurrence for permanent hearing loss and tinnitus in your study relative to those of the Accutane® study. If different, then labeling would need to address the observed difference.

Reviewer Comment: Unable to locate sponsor / DDDP response to this deficiency. DDDP will need to decide if the reported 18% - 19% of subjects evaluated for threshold shift is adequate sampling for safety decisions re potential for ototoxicity. However, the reported threshold shift results for the experimental subject group (2.3% of subjects) and control group (5.3% of subjects) is low. And, the absence of a significant difference between the two subject groups suggests that the experimental drug (CIP-ISOTRETINOIN) is no worse than that which is already being marketed.

**Def.#2.** You have proposed conducting Audiology tests by "an appropriately trained professional." However, the qualifications of the individuals providing the training have not been reported; nor has the training program been described. Thus, it remains unknown if a clinical audiologist will be involved with

subject assessments, staff training, or coordination of these activities with medical center personnel. Please provide the qualifications of those conducting audiology assessments and their associated training.

**Sponsor/DDDP Agreement:**

*Within the participating dermatology sites, research nurses and coordinators will be trained by trainers experienced in providing training on the (b) (4) Amplitude T series equipment. Automatic and manual modes of operation will be taught. Research staff will be tested on their ability to conduct screening audiograms on a minimum of two volunteers in addition to a selftest, in the presence of the trainer.*

Reviewer Comment: Accepted

**Def.#3.** You have proposed conducting audiology assessments only during screening or at the baseline visit and at week 20 or at the end of study visit,  $\pm 10$  days at end of study. However, hearing loss may already have occurred during this interval. No data were provided on the expected latency between drug administration and potential manifestation of hearing loss / tinnitus. Monitoring tests should be scheduled at intervals that will enable the earliest possible detection (within reason) of cochleotoxic effects. Further, subjects who complain of symptoms consistent with cochlear (or vestibular) damage should be seen immediately. The prospective assessment of hearing function is the only reliable method for detecting the presence of cochleotoxicity prior to symptomatic hearing loss. Thus, the testing timeline should be modified to include more frequent assessments. Alternatively, a rationale as to why more frequent assessment is not necessary should be provided.

Reviewer Comment: Unable to locate sponsor / DDDP response to this deficiency. However, the low percentage of subjects who experienced a threshold shift in the study as well as only one subject reporting vertigo eliminates the prior concern about the testing timeline.

**Def.#4.** The audiometric test instrumentation and test environment in which testing will occur has not been identified, e.g., audiometric sound booth. Nor have you reported the psychophysical method you intend to use for determining pure-tone thresholds. Please describe the test instrumentation, test environment, and the psychophysical method employed for threshold assessment. In addition, please identify the reference standards used to ensure instrumentation calibration and to ensure test environment uniformity across clinical sites (examples of appropriate standards<sup>1</sup>).

**Sponsor/DDDP Agreement:**

*Equipment used by the participating audiology clinics will be calibrated at least once annually according to the Standard Operating Procedures of the clinic. Audiometers and headphones used within the dermatology clinic will be supplied by (b) (4) Each participating site will receive the equipment (Amplitude T\_Series handheld unit and headphones) calibrated together along with an Audiometer Calibration Certificate providing the following information: model, serial number, S/N*

<sup>1</sup> ANSI S3.1-1999 (R 2003) Maximum Permissible Ambient Noise Levels for Audiometric Test Rooms  
ANSI S3.6-2004 American national Standard Specification for Audiometers  
ANSI S12.2-1995 (R 1999) Criteria for Evaluating Room Noise  
ANSI S3.21-2004 American National Standard Methods for Manual Pure-Tone Threshold Audiometry

*Left, S/N Right, Mic./Sensor Description, Coupler Description, S/N, Mic Cal Date, Type, and Calibration Information with Reference Standards.*

Reviewer Comment: Calibration concern was addressed. However, test environment (i.e., quiet room) uniformity was not evaluated. Even so, the absence of elevated low-frequency thresholds at screening / baseline suggest that ambient noise was minimal and did not confound test results.

**Def.#5.** You propose to obtain air conduction pure-tone thresholds at .5-, 1-, 2-, 3-, 4-, 6-, and 8 kHz to monitor for potential changes in hearing sensitivity. However, the available evidence indicates that high-frequency (9 kHz – 20 kHz) assessment is more sensitive for the earliest detection of ototoxic hearing loss. In addition, Otoacoustic emission (OAE) assessment is another audiologic measure that also provides an objective means of assessing cochlear function. As with high-frequency thresholds (9k Hz and above), OAEs allows early detection of ototoxicity-induced hearing loss, when compared to conventional audiometry (.5-8 kHz). Please include high-frequency threshold assessment and OAE assessment in the study protocol or provide your rationale for not doing so.

Reviewer Comment: Unable to locate sponsor / DDDP response to this deficiency. Although the number of subjects reported to have a permanent threshold shift is low based on testing up to 8000Hz, testing at higher frequencies may have identified additional threshold shifts. At this point, however, the issue is moot.

**Def.#6.** The purpose of baseline testing is to document the status of hearing prior to treatment. Even so, you have not included any assessment criteria to identify at-risk subjects for potential hearing loss due to experimental drug exposure, such as subjects with existing hearing loss, existing tinnitus, or possible progressive hearing loss. At-risk subjects should receive baseline evaluations that are as complete as possible, not just pure-tone air conduction testing, and include immittance and speech tests. Likewise, if subjects are included who currently have tinnitus, baseline assessment of its severity should be documented, e.g., administration of a tinnitus assessment questionnaire, such as the Tinnitus Handicap Inventory. Evaluation of tinnitus subsequent to treatment of the experimental drug should also be done.

Reviewer Comment: Unable to locate sponsor / DDDP response to this deficiency. However, the small number of subjects experiencing a significant threshold shift suggests that potential “at-risk subjects” did not experience negative outcomes.

## **XI. Conclusions**

CDER / DDDP will need to determine if the small number of subjects evaluated for auditory safety is adequate and representative of the overall study sample.

Adverse events related to the ear and labyrinth were reported in approximately 2 percent of the patients in each treatment group, and only a small number of patients experienced a significant threshold shift during the study period. Based on data presented in Table 12-21 (P. 175), 2 of 86 subjects in the CIP-ISOTRETINOIN group and 5 of 94 subjects in the Reference Product group experienced a threshold shift in either ear at end of the

treatment period. The seven subjects are listed in Data Listing 16.2.9.8.2 – Audiology Assessment, Patients with a Confirmed Threshold Shift.

Only one subject was reported as having a tinnitus complaint.

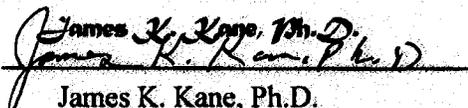
Overall, significant differences were not observed between the two study groups regarding changes in hearing sensitivity, subjective tinnitus or vestibular functionality.

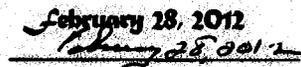
Labeling is consistent with the labeling associated with Accutane.

## **XII. Recommendations:**

1. Hearing safety decisions related to the experimental drug are based on a small percentage (~20%) of the total subjects participating in this study. CDER will need to decide if these small subgroups are sufficient for safety decisions.
2. CDER will need to determine if these subgroups represent 25% of the clinical sites as specified in the sponsor's protocol.

We do not know how these subgroups of subjects were sampled from the overall population. Even though the results of the hearing evaluations are consistent with what was accepted for the approved drug (Accutane), we are not convinced that the results from this small sample is sufficient to generalize the results to the overall study population or even to the general indicated population.

  
James K. Kane, Ph.D.  
Scientific Reviewer / Audiology

  
Date

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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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MATTHEW E WHITE

03/23/2012

Entered into DARRTS and signed on behalf of James Kane and Srinivas Nandkumar from  
CDRH/ODE/DOED/ENTB

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: March 22, 2012

Reviewer(s): Teresa McMillan, PharmD  
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD  
Division of Medication Error Prevention & Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention & Analysis

Drug Name(s): (b) (4) (Isotretinoin) Capsules  
10 mg, 20 mg, 30 mg, 40 mg

Application Type/Number: NDA 021951`

Applicant/sponsor: Cipher Pharmaceuticals, Inc.

OSE RCM #: 2012-224

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed blister labels, carton and insert labeling as well as the medication guide for (b) (4) (Isotretinoin) Capsules, NDA 021951, for areas of vulnerability that can lead to medication errors in response to a request from the Division of Dermatology and Dental Products (DDDP).

### 1.1 BACKGROUND OR REGULATORY HISTORY

On January 5, 2012, Cipher Pharmaceuticals, Inc. submitted a request to the Agency for an assessment of the proposed proprietary name (b) (4) which is currently being evaluated in a separate review (OSE #2012-47). This product will be distributed under the iPledge program which mandates the distribution of all currently marketed isotretinoin products (i.e. Amnesteem, Claravis, Myorisan, and Sotret) to help prevent the use of the drug during pregnancy due to the high risk of birth defects.

On February 3, 2012, Cipher Pharmaceuticals, Inc. submitted labels and labeling for the proposed proprietary name, (b) (4)

### 1.2 PRODUCT INFORMATION

- Active Ingredient: Isotretinoin
- Indication of Use: Severe recalcitrant nodular acne
- Route of Administration: Oral
- Dosage Form: Capsule
- Strength: 10 mg, 20 mg, 30 mg, 40 mg
- Dose and Frequency: 0.25 mg/kg to 0.5 mg/kg twice daily
- How Supplied: Blister packs of 10 capsules, 30 capsules per box
- Storage: Store at 20°-25°C (68°-77°F).Protect from light.

## 2 METHODS AND MATERIALS REVIEWED

Using the principles of Failure Mode and Effects Analysis<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels, Carton & Insert Labeling, Medication Guide submitted on February 3, 2012 ( see Appendix A and B for images, no image for insert labeling and medication guide)

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors because there is information displayed more prominently than the proprietary and established names and strength. Additionally, there is no statement alerting the dispenser to distribute with a medication guide. We recommend the following be implemented prior to approval:

#### A. All labels and labeling

Please remove all references to the phrase [REDACTED] (b) (4) from the labels and labeling. This product was found to be an immediate release and should be referred to as a capsule [REDACTED] (b) (4).

#### B. Blister Labels and Carton Labeling, 10 mg, 20 mg, 30 mg and 40 mg

1. Revise the presentation of the proprietary name, [REDACTED] (b) (4) from UPPERCASE to Title Case “[REDACTED] (b) (4)” to improve readability of the name.
2. Add the following statement at the top of your principal display panel where the company name is presently per 21 CFR 208.24(d):  
“Attention Pharmacist: Dispense with enclosed Medication Guide”
3. Your principal display panel is extremely crowded. To reduce clutter and allow room for the medication guide statement, we request you delete the company name on the principal display panel. This information is redundant and detracts from other important information such as the proprietary and established names and strength.
4. Ensure the established name is at least ½ size of proprietary name and has a commensurate prominence with proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).

#### C. Blister Labels, 10 mg, 20 mg, 30 mg, and 40 mg

1. Ensure the strength statement follows the proprietary and established names. Currently, the side panels and the lower right portion of the principal display panel only display the strength.
2. Decrease the size of the “Rx only” statement and relocate to the bottom of the principal display panel. As presented, it detracts from important information such as the strength.
3. Decrease the size of the statement “10 capsules prescription pack”. As presented, it detracts from the proprietary and established names as well as the strength.

#### D. Carton Labeling, 10 mg, 20 mg, 30 mg, and 40 mg

1. Decrease the size of the statement “30 capsules”. As presented, it detracts from the proprietary and established names as well as the strength.

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

**APPENDICES**

**APPENDIX A: BLISTER LABELS – 10 MG, 20 MG, 30 MG, 40 MG**

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(CCI/TS) Immediately Following this Page

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TERESA S MCMILLAN  
03/22/2012

LUBNA A MERCHANT  
03/22/2012

CAROL A HOLQUIST  
03/23/2012

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA  
CONSULT #11-305**

**Consultant Reviewer:** Gregory M. Dubitsky, M.D.  
Medical Officer  
Division of Psychiatry Products

**Consultation Requestor:** Mathew White  
Regulatory Project Manager  
Division of Dermatology and Dental Products

**Subject of Request:** NDA 21-951/CIP Isotretinoin Capsules

**Date of Request:** December 20, 2011

**Date Received:** December 20, 2011

**Desired Completion Date:** February 29, 2012

**Completion Date:** February 27, 2012

**I. Background**

Isotretinoin capsules are approved for the treatment of severe recalcitrant nodular acne. Labeling carries a (b) (4) warning which states that this drug may cause psychiatric reactions such as depression, psychosis and, rarely, suicidal ideation, suicide attempts, and suicide, and aggressive and/or violent behavior. Patients treated with isotretinoin capsules should be monitored for these psychiatric symptoms and be advised to discontinue the drug at once if such symptoms emerge. A brochure is available to assist prescribers in recognizing psychiatric disorders in adolescents and young adults.

The mechanism for the psychiatric effects of isotretinoin is not known. Isotretinoin (or 13-*cis*-retinoic acid) is isomerized in tissue to *trans*-retinoic acid, an endogenous regulator of gene expression in several brain regions to include the striatum, hippocampus, frontal cortex, and hypothalamus. Administration of isotretinoin and conversion to *trans*-retinoic acid is hypothesized to destabilize the balance of retinoic acid synthesis and breakdown and produce inappropriate gene transcription. In particular, there has been recent interest in the retinoic acid-regulated gene in the hypothalamus responsible for the expression of corticotrophin-releasing hormone, which in turn may contribute to hypothalamus-pituitary-adrenal (HPA) axis hyperactivity observed in depressed patients.<sup>1</sup>

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<sup>1</sup> Bremner JD, et al. Retinoic Acid and Affective Disorders: The Evidence for an Association. J Clin Psychiatry 2012;73:37-50.

The currently recommended treatment regimen for isotretinoin capsules is a dose of 0.5 to 1.0 mg/kg/day taken BID with food for 15 to 20 weeks.<sup>2</sup> Cipher Pharmaceuticals has submitted NDA 21-951 for a (b) (4) capsule formulation of isotretinoin (Cip-Isotretinoin) which may be taken with or without food.<sup>3</sup>

To support their application, Cipher conducted 13 Phase 1 studies comparing Cip-Isotretinoin with Accutane.<sup>4</sup> In addition, they conducted a Phase 3 randomized, double-blind, parallel group, non-inferiority trial (ISOCT.08.01) that compared Cip-Isotretinoin with a marketed formulation of isotretinoin as reference. There has been a concern that the enhanced bioavailability of Cip-Isotretinoin may produce a higher incidence of psychiatric adverse experiences than seen with marketed isotretinoin capsules. Thus, among the objectives of this trial was the evaluation of the safety profile for Cip-Isotretinoin compared to that of the reference drug. The Division of Dermatology and Dental Products (DDDP) has requested consultation with the Division of Psychiatry Products (DPP) for an assessment of the adequacy of psychiatric monitoring and the comparison of the psychiatric adverse event profiles in ISOCT.08.01 as well as Cipher's proposed labeling to describe psychiatric reactions.

As further background, the design of trial ISOCT.08.01 has been the subject of four previous consultations.<sup>5</sup> These consultative reviews included extensive discussion of patient selection criteria, particularly with respect to the inclusion of patients with a history of depression, and the choice of instruments for screening and monitoring treatment-emergent psychiatric adverse events.

## **II. Psychiatric Review of Trial ISOCT.08.01: "A Double-Blind, Randomized, Phase III Parallel Group Study Evaluating the Efficacy and Safety of CIP-Isotretinoin in Patients with Severe Recalcitrant Nodular Acne"**

### Study Design

The trial objective was to evaluate the safety and efficacy of CIP-Isotretinoin and a marketed generic formulation of isotretinoin in patients with severe, recalcitrant nodular acne. The two co-primary efficacy measures were the reduction in number of facial and truncal nodular lesions from baseline to week 20 and the proportion of patients with at least a 90% reduction in lesions.

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<sup>2</sup> The bioavailability of isotretinoin is reduced by about 60% in fasted versus fed conditions. Thus, isotretinoin capsules are taken with food.

<sup>3</sup> The sponsor states that under fasted conditions, the bioavailability of Cip-Isotretinoin is 30% lower than under fed conditions

<sup>4</sup> Until June 2009, isotretinoin capsules were marketed by Roche Pharmaceuticals as Accutane. Isotretinoin capsules are currently manufactured by a number of other companies, with the reference listed drug being Amnesteem, made by Mylan.

<sup>5</sup> DPP consult #11-045 by Greg Dubitsky (January 29, 2008), OSE/DEPI consult by Andrew Mosholder (April 2, 2008), DPP consult #11-082 by Victor Crentsil (August 25, 2008), and DPP consult #11-114 by Gwen Zornberg (March 5, 2009).

This trial was conducted at 49 sites: 38 sites in the U.S. and 11 in Canada.

This was a randomized, double-blind, active-control, parallel group trial that consisted of a 20 week treatment phase and a 4 week follow-up phase. Eligible patients were randomized to two groups, Cip-Isotretinoin or Reference Product, in a 1:1 ratio stratified by gender and study site.<sup>6</sup> Study medication was taken at an initial dose of approximately 0.5 mg/kg/day twice daily with meals for the first 4 weeks, then approximately 1.0 mg/kg/day twice daily with meals for 16 weeks.

Over-encapsulation was used to maintain blinding.

Psychiatric medication was not prohibited during the trial.

#### Inclusion/Exclusion Criteria

Patients were between the ages of 12 and 54 years with a diagnosis of severe recalcitrant nodular acne who had no previous retinoid exposure. Patients had to weigh between 40 and 110kg (88 to 242 lbs) and had to have 10 or more nodular lesions on the face and/or trunk.

Psychiatric exclusionary criteria at screening included the following:

- past or current psychotic symptoms. Patients with a history of major depression, mania, hypomania, or mixed mood episodes were not excluded unless the episode occurred in the preceding year.
- any suicidal behavior (i.e., attempts, interrupted attempts, aborted attempts, or other preparatory behavior) within the past year or serious suicidal ideation (with some intent to act with or without a specific plan) in the past year.

#### Psychiatric Evaluations

Cipher implemented a program to insure that each patient was evaluated by a mental health professional at each study visit for the purpose of assessing emergent psychiatric symptoms during the trial.

The Structured Clinical Interview for DSM-IV-Clinical Trials (SCID-CT) for major depressive episodes, mania, and psychosis was used to assess trial eligibility.

Psychiatric monitoring was performed with the following instruments:

- Patient Health Questionnaire-8 (PHQ-8) was used to detect a change in mental status indicative of a depressive disorder and to quantify spontaneous reports of depressive symptoms.

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<sup>6</sup> Accutane became unavailable prior to study commencement. Therefore, Amnesteem was selected as the Reference Product. To maintain a supply of study medication, a second marketed product, Clavaris, made by Barr Pharmaceuticals, was used as the Reference Product on a temporary basis.

- Columbia-Suicide Severity Rating Scale (C-SSRS) was used to monitor for suicidal ideation and behavior.
- Generalized Anxiety Disorder-7 (GAD-7) was used to detect clinical symptoms of generalized anxiety disorder and to quantify spontaneous reports of anxiety-related symptoms.
- A psychosis assessment was performed to monitor for emergent psychotic symptoms and based on responses to three questions.<sup>7</sup>

Copies of the PHQ-8, GAD-7, and psychosis assessment questions are provided in Appendix 1 of this review.

The schedule for psychiatric assessments is displayed in Table 1 below. A follow-up visit was conducted at week 24.

	Screening	Baseline	Week						
			2	4	8	12	16	20	24
SCID-CT	X								
C-SSRS	X	X	X	X	X	X	X	X	X
GAD-7		X		X	X	X	X	X	X
PHQ-8	X	X	X	X	X	X	X	X	X
Psychosis		X		X	X	X	X	X	X

All patient psychiatric assessments were performed remotely via telephone by a (b) (4) that specializes in conducting remote mental health assessments (b) (4). A total of 28 raters conducted all psychiatric assessments. All were mental health professionals, qualified by training to conduct assessments with the SCID-CT, PHQ-8, C-SSRS, GAD-7, and psychosis assessment.

Any patients presenting with psychiatric adverse events deemed clinically significant by the investigator were required to be evaluated by a local psychiatrist.

## Results

### *Description of the Patient Sample*

A total of 1265 patients were screened for this trial. The Intent-To-Treat sample consisted of 925 patients. The patient disposition is shown in Table 2 below.

<sup>7</sup> These questions were developed based on DSM-IV criteria, with FDA input.

<b>Table 2: Enumeration of Patients By Disposition</b>		
	<b>CIP-Isotretinoin</b>	<b>Reference Isotretinoin</b>
ITT	464	461
Week 20 Completers	403	410
Week 24 Completers	394	401
Dropouts (before week 24)	70	60
Reason for Dropout		
Adverse Event	19	15
Patient Withdrew Consent	15	15
Investigator's Discretion	1	2
Lost to Follow-up	20	16
Noncompliance	5	8
Other	10	4

Among the ITT patients, the two treatment groups were reasonably well balanced on various demographic characteristics at baseline (see Appendix 2 of this review). The groups were also similar in terms of psychiatric histories, as shown in Table 3. In the CIP-Isotretinoin group, 11.6% of patients had a history of a psychiatric disorder compared to 13.9% of Reference-treated patients.

<b>Table 3: Enumeration of Patients with a Psychiatric History<sup>8</sup></b>		
	<b>CIP-Isotretinoin (N=464)</b>	<b>Reference (N=461)</b>
Attention Deficit/Hyperactivity Disorder	23	24
Anxiety	14	19
Depression	14	17
Insomnia	9	14
Bipolar Disorder	1	2
Drug Abuse	1	2
Anxiety Disorder	2	0
Asberger's Syndrome	1	1
Bipolar I Disorder	1	1

I examined the proportions of patients who were using psychiatric medications prior to the study and concomitantly during the trial (as presented in study report Tables 14.1.5 and 14.4.2, respectively). There were no major differences in psychiatric drug use between the two randomized treatment groups.

Of the 925 patients who comprised the ITT sample, 924 patients were included in the safety analysis (464 were randomized to CIP-Isotretinoin and 460 to the Reference Product).

<sup>8</sup> Symptoms and disorders reported by more than one patient in the ITT.

### *Psychiatric Adverse Events*

Psychiatric adverse events were reported by 6.3% (29/464) of CIP-Isotretinoin patients and 5.9% (27/460) Reference Product patients. Table 4 enumerates these patients by MedDRA preferred term. The most commonly reported psychiatric adverse event was insomnia. Insomnia was not associated with mood or anxiety symptoms, as measured by the PHQ-8 and GAD-7. There were no major differences between treatment groups in the reporting frequency for any adverse event.

<b>MedDRA Preferred Term</b>	<b>CIP-Isotretinoin (N=464)</b>	<b>Reference (N=460)</b>
Insomnia	14	9
Anxiety	5	7
Depression	3	4
Attention deficit/hyperactivity disorder	2	1
Mood swings	0	3
Sleep disorder	2	1
Panic attack	2	0
Restlessness	1	1
Stress	1	1

There was one psychiatric adverse event classified as serious: an 18 year old white male who presented with substance abuse 23 days after his last dose of CIP-Isotretinoin (patient 01/001). He was hospitalized and subsequently "recovered."

Five patients in each treatment arm dropped out due to psychiatric symptoms. The events leading to dropout are shown in Table 5 below. Again, there were no major differences between the treatment groups. All events leading to dropout were known to have resolved except for depression in one patient who was lost to follow-up.

<sup>9</sup> For those adverse events reported by more than one patient in the safety population.

<b>MedDRA Preferred Term</b>	<b>CIP-Isotretinoin (N=464)</b>	<b>Reference (N=460)</b>
Anxiety	1	1
Depression	2	0
Emotional distress	0	1
Hallucination (auditory)	1	0
Insomnia	0	1
Mood swings	0	1
Obsessive thoughts	0	1
Panic attack	1	0

### *PHQ-8*

For each spontaneous report of depressed mood, the corresponding PHQ-8 was evaluated to determine if the total score was 10 or greater; a score of 10 was considered the threshold for clinically significant depression. Four patients taking CIP-Isotretinoin and 5 taking the Reference Product had a PHQ-8 total score of 10 or more at any visit.

The change from baseline to end of treatment in the PHQ-8 score was similar between the groups, as shown in Table 6.

	<b>CIP-Isotretinoin</b>		<b>Reference Product</b>	
	<b>Change</b>	<b>% Change<sup>10</sup></b>	<b>Change</b>	<b>% Change</b>
N	464	433	460	426
Mean (SD)	-0.05 (1.57)	-11.69 (72.3)	0.00 (1.89)	-10.41 (87.5)
Median	0.00	0.00	0.00	0.00

### *C-SSRS*

In all, 459 patients treated with CIP-Isotretinoin and 458 treated with the Reference Product responded to the C-SSRS questionnaire. No patients in either group responded with a "yes" to any suicidal behavior question at any post-baseline visit (completed suicide, suicide attempt, or preparatory actions toward imminent suicidal behavior).

A total of 11 patients reported suicidal ideation on the C-SSRS at some point post-baseline: 4 were treated with CIP-Isotretinoin and 7 with the Reference Product.<sup>11</sup> Enumeration of these patients by the most severe level of ideation is provided in Table 7. There was no major imbalance between the groups in terms

<sup>10</sup> Calculations of percentage change exclude those patients with a score of zero at baseline.

<sup>11</sup> Based on my examination of the file QCSSRS.xpt.

of level of suicidal ideation, with the lowest level of severity (wish to be dead) most common in both groups.

<b>Level of Suicidal Ideation</b>	<b>CIP-Isotretinoin (N=459)</b>	<b>Reference (N=458)</b>
Wish to be dead	3	5
Non-specific active suicidal thoughts	0	0
Active suicidal ideation without plan or intent	1	2
Active suicidal ideation with intent but no specific plan	0	0
Active suicidal ideation with intent and specific plan	0	0

#### *GAD-7*

For each spontaneous report of an anxiety-like symptom, the corresponding GAD-7 was evaluated to determine if the total score was 10 or greater; a score of 10 was considered the threshold for clinically significant anxiety. Two patients taking CIP-Isotretinoin and 4 taking the Reference Product had a PHQ-8 total score of 10 or more at any visit.

The change from baseline to end of treatment in the GAD-7 score was similar between the groups, as shown in Table 8.

	<b>CIP-Isotretinoin</b>		<b>Reference Product</b>	
	<b>Change</b>	<b>% Change<sup>12</sup></b>	<b>Change</b>	<b>% Change</b>
N	461	440	459	433
Mean (SD)	-0.19 (1.11)	-17.39 (46.9)	-0.22 (1.57)	-18.41 (49.5)
Median	0.00	0.00	0.00	0.00

#### *Psychosis Assessment*

Only one patient in each treatment group responded to at least one of the three psychosis assessment questions in the affirmative. Patient 43/038, treated with CIP-Isotretinoin, experienced auditory hallucinations, which were treated with quetiapine and olanzapine. In the Reference Product group, patient 06/001 experienced persecutory delusions at 2 unscheduled visits and other delusions at one of these visits. These were treated with pharmacotherapy and the patient's condition was improving.

<sup>12</sup> Calculations of percentage change exclude those patients with a score of zero at baseline.

### III. Labeling

Four sections of Cipher's proposed labeling contain language regarding psychiatric signs and symptoms associated with isotretinoin: Highlights (Warnings and Precautions), Warnings and Precautions (5.1.1), Adverse Reactions (6.10), and Patient Counseling Information (17.2). Each section is discussed below.

(b) (4)

#### 5 Warnings and Precautions (5.1.1)

This section contains essentially the same information contained in Amnesteem labeling. However, Cipher has modified the second sentence of this section:

(b) (4)

#### 6 Adverse Reactions (6.10)

This section appears to combine adverse reactions from clinical trials with those reported during postmarketing surveillance. It is recommended that the description of adverse reactions from clinical trials be presented separately from those reported spontaneously during postmarketing surveillance, if possible, in accordance with 21 CFR 201.57(c)(7)(ii)(B).

(b) (4)



Therefore, it is recommended that the first paragraph of this section be modified as follows:



#### **IV. Conclusions and Recommendations**

The psychiatric assessments performed in study ISOCT.08.01 appear to be adequate and are consistent with recommendations provided by DPP in the past. On the whole, there are no important differences between the psychiatric safety profiles of Cip-Isotretinoin and the Reference Product.

The exclusion of patients with an active or recent history of a mood disorder or suicidal ideation or behavior from study ISOCT.08.01 precludes any determination of whether Cip-Isotretinoin would be associated with a higher risk of treatment-emergent psychiatric symptoms in such patients compared to patients without such a history. Nonetheless, it seems probable that any risk differential would apply equally to both Cip-Isotretinoin and other isotretinoin products.

It is recommended that the sponsor implement certain revisions to the psychiatric sections of labeling, as documented above.

Please let us know if we may be of further assistance with this application.

## APPENDIX 1: Psychiatric Rating Instruments

### PHQ-8

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day	N/A
1. Little interest or pleasure in doing things	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Feeling down, depressed, or hopeless	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Trouble falling or staying asleep, or sleeping too much	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Feeling tired or having little energy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Poor appetite or overeating	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Trouble concentrating on things, such as reading the newspaper or watching television	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Responses are scored from 0 (not at all) to 3 (nearly every day).

## APPENDIX 1 (continued)

### GAD-7

Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day	N/A
1. Feeling nervous, anxious or on edge	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Not being able to stop or control worrying	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Worrying too much about different things	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Trouble relaxing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Being so restless that it is hard to sit still	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Becoming easily annoyed or irritable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Feeling afraid as if something awful might happen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Responses are scored from 0 (not at all) to 3 (nearly every day).

## **APPENDIX 1 (continued)**

### **Psychosis Assessment**

In the past month, have there been times that you felt that a group of people were plotting to cause you serious harm or injury?

Over the last month, have there been times when you felt that something strange was going on, something so strange that other people would find it very hard to believe?

Over the past month, have there been times when you heard or saw things that other people couldn't?

## APPENDIX 2: Baseline Demographic Characteristics

	CEP- ISOTRETINOIN (N = 464)	Reference Product (N = 461)	Overall (N = 925)
<b>Age (yr)</b>			
N	464	461	925
Mean (SD)	20.8 (7.5)	20.7 (6.8)	20.8 (7.2)
Median	18.0	18.0	18.0
Minimum, Maximum	12, 50	12, 52	12, 52
<b>Age Group - n (%) - year:</b>			
12-14	62 (13.4)	41 (8.9)	103 (11.1)
15-17	143 (30.8)	151 (32.8)	294 (31.6)
18-29	203 (43.8)	212 (46.0)	415 (44.9)
30-44	47 (10.1)	55 (11.9)	102 (11.0)
≥45	9 (1.9)	2 (0.4)	11 (1.2)
<b>Gender - n (%)</b>			
Male	277 (59.7)	283 (61.4)	560 (60.5)
Female	187 (40.3)	178 (38.6)	365 (39.5)
<b>Geographic Region - n (%)</b>			
US	380 (81.9)	373 (80.9)	753 (81.4)
Canada	84 (18.1)	88 (19.1)	172 (18.6)
<b>Ethnicity - n (%)</b>			
Hispanic	39 (12.7)	63 (13.7)	122 (13.2)
Non-Hispanic	405 (87.3)	398 (86.3)	803 (86.8)
<b>Race - n (%)</b>			
White	399 (86.0)	404 (87.6)	803 (86.8)
Black or African American	28 (6.0)	14 (3.0)	42 (4.5)
Asian	27 (5.8)	26 (5.6)	53 (5.7)
Native Hawaiian or Other Pacific Islander	2 (0.4)	1 (0.2)	3 (0.3)
North American Indian or Alaskan Native	2 (0.4)	4 (0.9)	6 (0.6)
Other	6 (1.3)	12 (2.6)	18 (1.9)

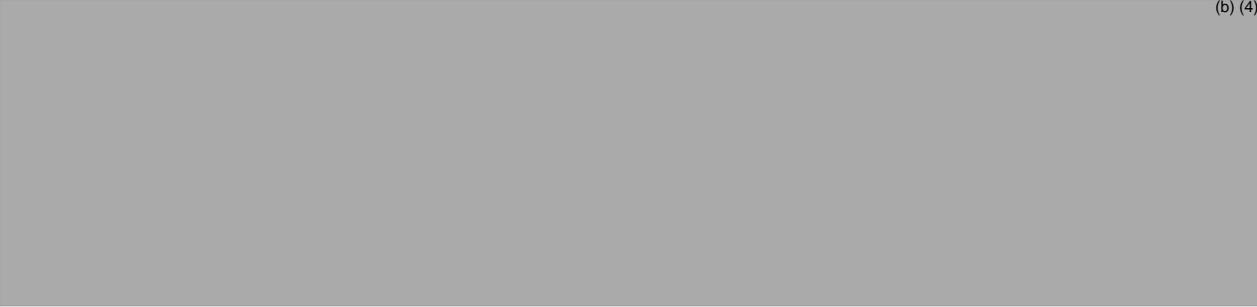
## APPENDIX 3

### Psychiatric Adverse Reactions

### Cip-Isotretinoin vs Amnesteem Labeling

#### Cip-Isotretinoin

(b) (4)



#### Amnesteem

**Psychiatric:** suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see WARNINGS: Psychiatric Disorders), emotional instability  
Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

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/s/  
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GREGORY M DUBITSKY  
02/27/2012

JING ZHANG  
02/27/2012

THOMAS P LAUGHREN  
02/27/2012

Medical Officer's Review of NDA 21-951  
Request for Ophthalmology Consultation

NDA 21-951

**Submission Date:** 11/29/11  
**Consultation Date:** 12/20/11  
**Review Date:** 2/15/12

**Applicant:**

Cipher Pharmaceuticals, Inc  
5650 Tomken Road, Unit 16  
Mississauga  
Ontario L4W 4P1  
Canada

**Drug:**

Cip-Isotretinoin capsules

**Proposed Indication:**

Severe recalcitrant nodular acne

**Consultation Comments/Special Instructions:**

On April 25, 2007, the Agency sent Cipher Pharmaceuticals an approvable letter for NDA 021951 Cip-isotretinoin capsules. The complete response for NDA 021951 was received on November 29, 2011. The sponsor has conducted a Phase 3 active controlled trial between Cip-isotretinoin and a generic isotretinoin according to the terms of a SPA agreed upon with the Agency on April 8, 2009. This trial was to evaluate that Cip-isotretinoin, because of the difference in its bioavailability, does not have a worse safety profile than the innovator drug product, isotretinoin. This is an electronic submission. Meeting minutes and correspondence can be found in Module 1.6.3 and the body of the study report can be found in Module 5.3.5.1.3. Please comment on any relevant section of the label.

Please evaluate the data for the effects of the drug products on vision in this trial and comment on the adequacy of the administered tools and results. Comment also on the comparison of the adverse event profile between the two drug products.

The resubmission is available at \\CDSESUB1\EVSPROD\NDA021951\021951.enx (dated 11/28/11).

**Reviewer's Comments:**

*With the exception of the Ophthalmologic examinations, the evaluation of the trial design is deferred to the primary review team. The submitted protocol was previously reviewed by this medical officer under IND 64,927 on 8/19/08 and 3/11/09.*

**Submitted:**

Submitted is the clinical study report for Protocol # ISOCT.08.01, A Double-Blind, Randomized, Phase III, Parallel Group Study Evaluating the Efficacy and Safety of CIP- ISOTRETINOIN in Patients with Severe Recalcitrant Nodular Acne.

**Reviewer's Comments:**

*Regarding Protocol # ISOCT.08.01, A Double-Blind, Randomized, Phase III, Parallel Group Study Evaluating the Efficacy and Safety of CIP- ISOTRETINOIN in Patients with Severe Recalcitrant Nodular Acne:*

- 1) *As designed and conducted, this protocol did not provide adequate ocular monitoring of study subjects; the ocular safety of the study treatments were not adequately addressed. To evaluate ocular safety, the protocol would have needed to include assessments of the conjunctiva, cornea, lens, optic nerve, retina, color vision, dark adaptation, retinal electrical activity, and tear production.*

*The potential adverse reactions from clinical studies and post-marketing experience of marketed isotretinoin cited in Section 8.1 of the protocol related to vision (e.g. corneal opacities, decreased night vision, cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, and visual disturbances) were not adequately assessed in study subjects.*

- 2) *The analyses provided in the Clinical Study Report (CSR) relating to visual acuity and adverse events (ocular) are not correctly performed.*

- a. *Visual acuity assessed on the Snellen Eye Chart is reported as a "line shift" away/towards 20/20. This is incorrect because 20/20 is not the best vision that can be achieved. Some line shifts from 20/20 represent improvement in visual acuity and some line shifts represent an impairment of visual acuity. It is important to count improvement in visual acuity as an improvement and distinguish it from a worsening of vision.*

*Snellen Visual acuity is best analyzed by conversion to logMAR, then reporting -0.3, -0.2, -0.1, 0, 0.1, 0.2, 0.3 and >0.3 log changes. The Snellen acuity for each subject on each visit is recorded so it should be converted by the applicant and analyzed.*

- b. *When data listings are reviewed, there are numerous instances where decreased vision under dim light condition is coded as "visual acuity reduced." This inaccurately captures the number of reported cases of both visual acuity reduction and night blindness. In addition, as an adverse event, it is not clear how Xerophthalmia is being distinguished from Dry Eye or how conjunctival hyperemia is being distinguished from conjunctivitis. The incidence of eye events should be recalculated by the applicant.*
- c. *The protocol states that patients who present with issues requiring a full ophthalmic work-up will be referred to the patients own or a local ophthalmologist recommended by the investigator for further evaluation. Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the night blindness.*

*Two subjects in the Cip-isotretinoin group discontinued due to eye events (night blindness; punctate keratitis), but there is no discussion or analysis within the study report indicating the number of subjects requiring a full ophthalmic*

*workup or what was found during the full ophthalmic workup. The applicant should provide this information. If only two subjects were referred for full evaluation, the applicant should explain why patients were referred for evaluation, but the evaluation was not analyzed.*

*The CSR states that follow-up reports of available [ophthalmic] evaluations were included in the patient's study record. This information does not appear to be present in Appendix 16.3.1 for subjects 23/004 and 43/002. The applicant should provide the exact location of the follow-up reports of available ophthalmic evaluations for these subjects.*

### **Summary Statement/ Recommended Action:**

#### Summary Statements:

- 1) As designed and conducted, this protocol did not provide adequate ocular monitoring of study subjects; the ocular safety of the study treatments were not adequately addressed. To evaluate ocular safety, the protocol would have needed to include assessments of the conjunctiva, cornea, lens, optic nerve, retina, color vision, dark adaptation, retinal electrical activity, and tear production.

The potential adverse reactions from clinical studies and post-marketing experience of marketed isotretinoin cited in Section 8.1 of the protocol related to vision (e.g. corneal opacities, decreased night vision, cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, and visual disturbances) were not adequately assessed in study subjects.

- 2) The analyses provided in the Clinical Study Report (CSR) relating to visual acuity and adverse events (ocular) are not correctly performed.

#### Items to be addressed by the Applicant:

- a. Visual acuity assessed on the Snellen Eye Chart is reported as a "line shift" away/towards 20/20. This is incorrect because 20/20 is not the best vision that can be achieved. Some line shifts from 20/20 represent improvement in visual acuity and some line shifts represent an impairment of visual acuity. It is important to count improvement in visual acuity as an improvement and distinguish it from a worsening of vision.

Snellen Visual acuity is best analyzed by conversion to logMAR, then reporting -0.3, -0.2, -0.1, 0, 0.1, 0.2, 0.3 and >0.3 log changes. The Snellen acuity for each subject on each visit is recorded so it should be converted by the applicant and analyzed.

- b. When data listings are reviewed, there are numerous instances where decreased vision under dim light condition is coded as "visual acuity reduced." This inaccurately captures the number of reported cases of both visual acuity reduction and night blindness. In addition, as an adverse event, it is not clear how Xerophthalmia is being distinguished from Dry Eye or how conjunctival

hyperemia is being distinguished from conjunctivitis. The incidence of eye events should be recalculated by the applicant.

- c. The protocol states that patients who present with issues requiring a full ophthalmic work-up will be referred to the patients own or a local ophthalmologist recommended by the investigator for further evaluation. Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the night blindness.

Two subjects in the Cip-isotretinoin group discontinued due to eye events (night blindness; punctate keratitis), but there is no discussion or analysis within the study report indication the number of subjects requiring a full ophthalmic workup or what was found during the full ophthalmic workup. The applicant should provide this information. If only two subjects were referred for full evaluation, the applicant should explain why patients were referred for evaluation, but the evaluation was not analyzed.

The CSR states that follow-up reports of available [ophthalmic] evaluations were included in the patient's study record. This information does not appear to be present in Appendix 16.3.1 for subjects 23/004 and 43/002. The applicant should provide the exact location of the follow-up reports of available ophthalmic evaluations for these subjects.

Labeling:

DTOP will continue to work with the Division of Dermatology and Dental Drug Products on the product labeling for Cip-isotretinoin capsules and will attend the scheduled labeling meetings.

William M. Boyd, M.D.  
Clinical Team Leader

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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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WILLIAM M BOYD  
02/21/2012

WILEY A CHAMBERS  
02/21/2012

**Division of Dermatology and Dental Products**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** NDA 021951

**Name of Drug:** (CIP-isotretinoin) Capsules, 10 mg, 20 mg, 30 mg, 40 mg

**Applicant:** Cipher Pharmaceuticals

**Labeling Reviewed**

**Submission Date:** 11/29/11

**Receipt Date:** 11/29/11

**Background and Summary Description:**

A class-2 resubmission for NDA 021951 for (CIP-isotretinoin) Capsules was received on 11/29/2011. This NDA was submitted pursuant to 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with Accutane (isotretinoin) as the reference listed drug. Proposed labeling in PLR format was included with the resubmission.

**Review**

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages of the Selected Requirements for Prescribing Information (SRPI) with an "X."

The labeling issues are also described below:

**Highlights of Prescribing Information**

- The highlights section is not limited to one-half page in length.
- Indications and Usage:
  - the established pharmacologic class is not listed
- Contraindications:
  - Lists theoretical possibilities (b) (4)
- Adverse Reactions:

- The statement “To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy, Inc. at 1-800-406-7984 or iPLEDGE at (1-866-495-0654 and [www.ipledgeprogram.com](http://www.ipledgeprogram.com)) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).” should be bolded.

**Full Prescribing Information**

- **Boxed Warning:**
  - The boxed warning is located under Section 4 “Contraindications.” The boxed warning should be located above Section 1 “Indications and Usage” and formatted per 21 CFR 201.57(c)(1).
- **Adverse Reactions:**
  - The “Clinical Trials” and “Postmarketing Experience” subsections are not separate in accordance with 21 CFR 201.57(c)(7).
  - The following statement does not precede the presentation of adverse reactions in the “Clinical Trials Experience” subsection:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - The “Postmarketing Experience” subsection does not include the following statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
- **Patient Counseling Information:**
  - Does not reference FDA-approved patient labeling and does not include the statement “See FDA-approved patient labeling (Medication Guide)” at the beginning of section 17.

**Recommendations**

All labeling issues identified on the following pages with an “X” and described above will be conveyed to the applicant in an information request letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by February XX, 2012. The resubmitted labeling will be used for further labeling discussions.

Matthew White

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**
  - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
  - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - All contraindications listed in the FPI must also be listed in HL.
  - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)” must be present. Only include toll-free numbers.**
- **Patient Counseling Information Statement**
  - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”
- **Revision Date**
  - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

## CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA

### CONSULT # 11082

Consultant Reviewer: Victor Crentsil, M.D., M.H.S

Consultation Requester: Jill Lindstrom, MD (Team Leader)  
Elaine R. Smoot (RPM)  
Division of Dermatology and Dental Products

Subject: CIP-Isotretinon Capsules

Date Received: July 14, 2008

#### **I. Background**

CIP-Isotretinoin, a new oral formulation of isotretinoin, received an approvable letter from FDA on April 25, 2007. Unlike the currently marketed forms of isotretinoin (e.g., Accutane<sup>®</sup>), which are more bioavailable when taken postprandially compared to the fasting state, CIP-Isotretinoin has an enhanced bioavailability that is independent of the fed or fasted state. Isotretinoin has been linked with a variety of psychiatric adverse events (AEs), including depression, psychosis, and suicidality (suicidal ideation, suicide attempts and completed suicides). Due to the enhanced bioavailability of CIP-Isotretinoin, there is a concern that it may be associated with an increased occurrence of psychiatric AEs including suicidality. Such a concern is based on a clinical trial report that Roche's micronized formulation of isotretinoin, which had a bioavailability unaffected by food intake, reported a higher proportion of psychiatric AEs compared with the marketed Accutane<sup>®</sup> (1). The Division of Dermatology and Dental Products (DDDP) has requested that the sponsor of CIP-Isotretinoin (Cipher Pharmaceuticals, Inc.) conduct a clinical safety study as a condition of approval.

FDA met with the sponsor on January 28, 2008 to address the Agency's concerns regarding the safety of CIP-Isotretinoin. The inadequacy of assessment of neuropsychiatric events and, specifically, the insufficiency of the Beck depression scale as the sole psychiatric evaluation instrument was expressed by the Agency. In addition to recommending a schedule and time table for assessing potential neuropsychiatric events, FDA also recommended the addition of mental health clinicians as investigators.

To address the concerns expressed by FDA, the sponsor has submitted protocols for further studies to evaluate the safety of CIP-Isotretinoin for the Agency's assessment. DDDP has consulted Division of Psychiatry Products (DPP) twice for evaluation of the proposed study design and the psychiatric screening instrument(s). In response to the first consult, the protocol synopsis had been reviewed by DPP (Reviewer- Gregory M. Dubitsky, MD; Consult # 11045; Date: 1/29/08). The second consult relates to the review of the full study protocol. It must be noted that DPP has also participated in two internal

meetings (7/16/08 and 7/29/08) and one sponsor meeting (8/06/08) as part of the second consult. Dr Andrew Mosholder (Office of Surveillance and Epidemiology) was present at the 7/16/08 and 8/06/08 meetings, due to his long-term involvement with isotretinoin-related safety issues. The details of the recommendations of DPP discussed at all the meetings are embodied in this consult.

## **II. Consultation Request by Division of Dermatology and Dental Products**

DDDP has requested for DPP to review and comment on the proposed study design and the psychiatric/depression screening instruments. DDDP also posed the following specific question: “Are the psychiatric/depression screening instruments sufficient to protect subject safety and to detect a safety signal for depression and suicidality?”

## **III. Review of the Submitted Protocol and Psychiatric Monitoring Plan**

### *Clinical Protocol*

The proposed study is a multicenter, randomized (1:1), double-blind, active-controlled, parallel group design consisting of a 20-week treatment phase followed by a 4-week follow-up period. The objectives of the trial are: to compare the efficacy and safety of CIP-Isotretinoin to Accutane<sup>®</sup> (both administered as 10-mg or 20-mg capsules twice daily with food) and to evaluate the safety profile of CIP-Isotretinoin. The sponsor plans to not use a non-isotretinoin control because of potential study unblinding from distinct manifestations associated with isotretinoin use such as cheilitis. The sponsor expects to enroll approximately 800 males and females aged 12 to 55 years diagnosed with severe recalcitrant nodular acne at 50 study sites in the United States and Canada. A major exclusion criterion is a physician-diagnosed mood disorder. Dosing will be weight based, with a regimen consisting of 0.5 mg/kg/day for the first 4 weeks then 1 mg/kg/day for the remaining period for both drugs. The subjects will be re-evaluated 2 weeks and 4 weeks post-randomization and then 4-weekly thereafter. Psychiatric assessments will be performed with MINI International Neuropsychiatric Interview (MINI-Plus) during the screening period and Patient Health Questionnaire-9 [PHQ-9] during the treatment phase.

Safety assessments include psychiatric evaluations, clinical laboratory testing, physical examinations, musculoskeletal survey, bone mineral density assessments, and collection of data on AEs and concomitant medications. The psychiatric evaluations will consist of the use of MINI-Plus to identify potential subjects with major depressive disorder (MDD) and suicidal ideation during the screening phase. In addition, PHQ-9 will be administered at baseline and monthly thereafter throughout the study to document and monitor for emergent or alteration in depressive symptoms and emergence of suicidal ideation.

The sample size of the study was estimated to be 350 per arm ( for a target of 700 completers) and the sponsor performed power calculations assuming the background rate of depression in the general population to be 10%, using the rate of MDD in Accutane<sup>®</sup> as their non-inferiority margin and a one-sided Type I error rate of 0.025. The sponsor also reported sample sizes that may be needed to evaluate whether CIP-Isotretinoin is

non-inferior to Accutane<sup>®</sup> spontaneous reports of AEs of psychiatric events such as depression.

#### Psychiatric Monitoring Plan

The psychiatric monitoring plan will consist of the use of MINI-Plus and PHQ-9 instruments. MINI-Plus will be used to identify and exclude potential subjects with MDD and suicidal ideation during the screening phase and PHQ-9 to document and monitor for emergence or alteration in depressive symptoms and evaluation for suicidal ideation.

MINI-Plus [English Version 5.0.0]: MINI-Plus is a more detailed version of the original MINI instrument. MINI is an instrument which entails a brief structured interview for major Axis I psychiatric disorders in ICD-10 and DSM-IV. MINI-Plus is divided into modules corresponding to the various diagnostic categories; the responses are rated as “Yes or No”, according to the clinical judgment of the rater. It can be administered by a trained non-clinician and the median duration of administration is 15 minutes. MINI-Plus has questions to investigate the contribution of organic disease, drugs and alcohol to the psychiatric manifestations under investigation. The sponsor plans to administer Module A (Major Depressive Episode) and Module C (Suicidality).

Patient Health Questionnaire-9 [PHQ-9]: PHQ-9 is a 9-item, patient-reported depression scale specifically developed for use in primary care settings. The 9 items were adopted from the nine DSM-IV symptoms and signs of major depression. PHQ-9 is suggested to be used as a diagnostic instrument and a tool for monitoring treatment. The possible scores range from 0 to 27, with higher scores correlating with increased severity of depression. For monitoring of depressive symptoms, PHQ-9 scores of 15-19 suggest moderately severe major depression and  $\geq 20$  – severe major depression. To monitor treatment of depression, a  $\geq 5$  point drop in PHQ-9 score is suggestive of adequate response.

## **IV. Evaluation of Clinical Protocol and Psychiatric Monitoring Plan**

### ***A. Evaluation of Clinical Protocol/Study Design***

Overall, the protocol does not primarily focus on the safety of isotretinoin as desired by FDA, lacks a plan for screening or follow-up for psychotic manifestations, and excludes subjects with a history of mood disorders (which can reduce the generalizability of the results of the study). The psychiatric manifestations associated with isotretinoin are depression, psychosis, and suicidality (suicidal ideation, suicide attempts and completed suicides); however, the sponsor’s screening and monitoring plan is limited to depression and suicidal ideation, without evaluation for other dimensions of suicidality such as suicidal attempts, etc.

By excluding subjects with a history of mood disorders, the utility of the results of the study may be limited. First, a mood disorder is not a contraindication to isotretinoin use, thus patients with a history of a mood disorder is likely to be exposed in clinical practice. Second, mood disorders such as depression are more prevalent in the acne population

more than the general population; hence, the likelihood of a patient with a history of a mood disorder been exposed to isotretinoin is high. With their exclusion for this study, assuming this study does not show any difference between CIP-Isotretinoin and Accutane<sup>®</sup> with regard to psychiatric AEs, the interpretation of the study will be limited to a population without mood disorders and will not contribute much needed information to the critical question of the differential risk for psychiatric AEs in the presence of a history of a mood disorder. To avoid such a limited utility of the study, inclusion of patients with a history of mood disorders (excluding patients with active mood disorders) and performing subgroup analyses evaluating the risk of psychiatric AEs in the presence or absence of mood disorders, will be a more prudent approach.

Under the Section 11.1 of the study protocol (Study Discontinuation)- it is stated that obtaining a score suggestive of major depression on the PHQ-9 will not in itself be a criteria for discontinuation from the study because of possible false positivity. This is a problem because regardless of the instrument used, manifestations resulting in a significant score likely places the subject in a higher risk category for developing a psychiatric AE and continued exposure to a drug that has been associated with suicidality may be unsafe. In the interest of patient safety, regardless of the monitoring instrument used, a score suggestive of an active mood disorder should precipitate the discontinuation of the subject from the study and prompt evaluation by a mental health professional.

For determination of the appropriate sample size for this study, it is noted that the sponsor assumed a background rate of MDD to be 10% (i.e., the rate in the general population) and a non-inferiority margin of 5% (i.e., an assumption of the incidence of MDD in the Accutane<sup>®</sup> group). We suggest that the appropriate background rate to use is the prevalence of depression in acne patients, which is higher than 10%, and probably 18% (2). We also suggest the appropriate non-inferiority margin should probably be 1.6% - corresponding to the incidence of newly diagnosed depression in nodulocystic acne patients treated with isotretinoin (3). Please consult with biometrics for the appropriate background rate and inferiority margin as well as determination of the appropriate sample size necessary to prevent or minimize the type II error.

## ***B. Evaluation of Psychiatric Monitoring Plan/Instruments***

### ***MINI-Plus***

Although MINI-Plus is useful and validated for the diagnosis of depression in research studies, the modules proposed to be used by the sponsor in the psychiatric monitoring plan does not screen the prospective subjects for psychotic disorders. Therefore, addition of MINI modules that screen for psychiatric manifestations other than depressive episode and suicidality will be necessary for the study.

### ***PHQ-9***

Although use of PHQ-9 as a monitoring tool for this study is not objectionable, it has a variety of weaknesses for the proposed study worth mentioning. First, PHQ-9 only monitors for depression and is not useful for the other psychiatric AEs (e.g., psychotic symptoms) that will need surveillance for this study. PHQ-9 also seems to be inadequate

for suicidality since only a single item (item i) explores suicidal thought and not suicidal attempts, etc. Second, for major depression, the sensitivity of PHQ among dermatology patients was low at 55% [4, 5]. Such a low sensitivity suggests an appreciable false negativity rate; and this may be a problem for the proposed study. As Dr Woodcock stated in her December 2002 statement to the US House of Representatives (as cited by the sponsor) that patients who may need isotretinoin may not verbalize their psychiatric symptoms so as to get a drug that they may believe will be efficacious for their acne so that the chance of false negativity in a study with isotretinoin for acne will be high. Thus, the sensitivity of PHQ-9 is likely to be even lower for a population likely to have a high false negative rate for psychiatric symptomatology. This low sensitivity is likely to bias any difference between depressive symptoms between CIP-isotretinoin and Accutane<sup>®</sup> to the null because of possible under ascertainment of psychiatric AEs in both groups. Third, PHQ-9 was designed for assessment of symptoms over the preceding 2 weeks; hence, its monthly use in the proposed study may further affect its sensitivity in a manner that is difficult to predict but likely to further lower sensitivity. Fourth, for scoring, the distinction between the categories “several days” and “more than half the days” is unclear and subject to varied interpretation and increasing imprecision or variability. Despite the above issues PHQ-9 is considered a useful instrument for diagnosing and monitoring for changes in severity of depression in primary care settings and may be used for the study with the above potential pitfalls in mind.

#### ***Other comments***

At the August 6 meeting, the sponsor agreed to consider inclusion of subjects with a past history of a mood disorder (without an active mood disorder) and they will submit inclusion/exclusion criteria for review. The sponsor also agreed to include a MINI-plus module that screens for psychotic disorders including bipolar disorder (See final meeting minutes for more details). In addition, the following are responses to questions asked at or after the August 6, 2008 meeting:

#### **1. Can the sponsor revert to the Beck Depression Instrument (BDI) or use other instruments in place of PHQ-9?**

*Response: The sponsor may use any instrument for the study as long as it has a demonstrated validity and assay sensitivity for the intended purpose. In addition, the rationale for use should be acceptable. Whether the instrument obtains the data by subject self-report or is clinician-administered is not a critical issue since both types of instruments have their strengths and weaknesses. As stated in our previous consult authored by Dr Gregory M. Dubitsky (1/29/08), BDI may be acceptable for screening and monitoring of depressive symptomatology only. Thus, BDI has not been found to be useful for screening and monitoring for other psychiatric symptomatology other than depression.*

**2. Can the last question on PHQ-9 (item i) be used to screen or monitor subjects for suicidality and only those that answer “yes” be referred to a mental health professional for the other scales for suicidality, i.e., C-SSRS and C-CASA be administered?**

*Response:* The last question on PHQ-9 (item i) is- “Thoughts that you would be better off dead or of hurting yourself in some way.” This question screens or monitors for only suicidal ideation, at best. It does not screen or monitor for suicidal behavior or other dimensions of suicidality; thus, it is insufficient for screening or monitoring subjects for suicidality. Therefore, use of C-SSRS is the optimal approach to screen/monitor for the emergence of the spectrum of suicidal manifestations and C-CASA to classify suicidal manifestations. Both instruments should be administered at each visit and not only after an affirmative response is obtained for PHQ-9 item i.

**3. Should the frequency of evaluation for psychiatric adverse effects be every two weeks?**

*Response:* Evaluation for psychiatric adverse effects every four weeks as planned in the study is adequate as long as subjects will be instructed to contact the investigator promptly if they develop substantial symptoms of depression, suicidality, mania, hostility, anxiety, psychosis, or cognitive decline between visits.

## **V. Conclusions and Recommendations**

### ***Conclusions***

The submitted protocol has limitations that we recommend should be addressed. The proposed studies lack a plan for screening or follow-up for psychotic manifestations and the full spectrum of suicidality associated with isotretinoin use as well as a safe plan for discontinuation from the study. The proposed psychiatric screening instruments are insufficient to protect subject safety and to detect a safety signal for the spectrum of psychiatric adverse events associated with isotretinoin. The sample size needs to be re-evaluated, using valid and reliable estimates.

### ***Recommendations***

1. We find the exclusion of patients with an active mood disorder as well as those with a past history of suicidality not objectionable. However, to enhance the generalizability of the results of the proposed study, we recommend that subjects with a history of major depressive disorder and dysthymia should not be excluded.
2. We have no objection to the use of the MINI-Plus modules for major depressive episode and suicidality in screening subjects. We suggest the addition of other MINI-Plus modules, such as the screens for psychotic disorders.

3. The PHQ-9 is considered a useful instrument for diagnosing and monitoring for changes in severity of depression in primary care settings. To improve the detection of other psychiatric symptomatology, we recommend that the sponsor consider addition of the Brief Symptom Inventory (BSI-53) [See <http://www.pearsonassessments.com/tests/bsi.htm> for more information on the BSI-53]. We recommend prompt psychiatric referral if any subject meets one of the following criteria: a) a 25% or greater increase from baseline in the subscore for any of the nine psychopathology domains or b) an increase of at least two points or a subscore greater than or equal to three in the depression, hostility, or psychoticism domains. For PHQ-9, subjects who score  $\geq 15$  or a score of  $\geq 1$  on suicide-related question [Q.1(i)] at baseline or at any time during the trial monitoring should be discontinued from the study and promptly evaluated by a mental health professional.
4. We recommend the use of an adequate instrument to screen for and monitor the emergence of the spectrum of suicidal manifestations, such as the Columbia-Suicide Severity Rating Scale (C-SSRS). We strongly recommend use of the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to classify adverse events.
5. Since visits will occur monthly, subjects should be instructed to contact the investigator promptly if they develop substantial symptoms of depression, suicidality, mania, hostility, anxiety, psychosis, or cognitive decline between visits. We also recommend that during the conduct of the study, subjects who develop scores on any monitoring instrument suggestive of an active mood disorder should be discontinued from the study and promptly (i.e., before the subject leaves the study site) evaluated by a mental health professional.
6. There are different approaches to maximize the accuracy and reliability of psychiatric ratings in a dermatology practice population. As one approach, the sponsor may consider using an Interactive Voice Response System (IVRS) for patient self-report on symptoms of suicidal ideation or behavior. Another approach would be the use of a Centralized Expert Rating System to optimize subject screening and monitoring for psychiatric manifestations for all study sites. Both IVRS and centralized expert rating systems utilize remote methods. As a result, they should not replace the necessary vigilance of clinical investigators to avoid the emergence or worsening of adverse psychiatric manifestations such as suicidality.

## References

1. Strauss JS, et al (2001): Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: A randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol*; 45:196-207
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Victor Crentsil, M.D., M.H.S.

August 25, 2008

Clinical Reviewer

FDA CDER ODEI DPP HFD 130

cc: IND 64,927  
NDA 21-951  
HFD 130  
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G. Zornberg  
M. Mathis  
T. Laughren  
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E. Smoot

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Dr. Crentsil and I discussed DPP conclusions and recommendations  
for the study protocol with Dr. Laughren today  
who had also approved our preliminary comments sent  
on 31 July 2008 to DDDP before the  
meeting between DDDP and the sponsor.

Thomas Laughren  
8/28/2008 10:12:31 AM  
MEDICAL OFFICER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 2, 2008  
To: Susan Walker, M.D.  
Director, Division of Dermatology and Dental Products  
Thru: Rita Ouellet-Hellstrom, Ph.D., M.P.H.  
Acting Team Leader, Division of Epidemiology  
Thru: Solomon Iyasu, M.D., M.P.H.  
Director, Division of Epidemiology  
From: Andrew Mosholder, M.D., M.P.H.  
Medical Officer, Division of Epidemiology  
Subject: Neuropsychiatric assessments in isotretinoin clinical studies  
Drug Name(s): CIP-Isotretinoin  
Application Type/Number: NDA 21-951  
Submission Date: January 11, 2008  
Applicant/sponsor: Cipher Pharmaceuticals, Inc.  
OSE RCM #: 2008-60

## **1 INTRODUCTION**

Concerns have been raised regarding the neuropsychiatric effects of retinoid compounds for many years. Isotretinoin, marketed for the treatment of severe recalcitrant nodular acne, carries labeling warning of potential neuropsychiatric effects; however, systematically collected data that would establish a causal relationship has been lacking. Marketed isotretinoin products are to be taken with food because of severely limited bioavailability when taken in a fasted state. Cipher is developing a new formulation of isotretinoin with bioavailability similar for fed or fasting states. It is assumed that patients do not always follow the instructions about taking marketed Accutane with food, thereby sacrificing some bioavailability. As this would not apply to the new Cipher formulation, there are concerns that exposures in clinical use may be higher with the new formulation than with the existing marketed isotretinoin products, with correspondingly greater toxicities.

There is a precedent for this concern. The innovator sponsor for isotretinoin, Roche (manufacturer of Accutane), developed a micronized formulation of isotretinoin with bioavailability relatively unaffected by food intake. A 20-week clinical trial comparing Roche's new formulation to marketed Accutane (n=300 per arm) showed a much higher proportion of

patients receiving the new food-independent formulation experienced neuropsychiatric events (11/300 with the new formulation versus 1/300 with Accutane).<sup>1</sup>

The Agency has requested that Cipher Pharmaceuticals, the sponsor of CIP-Isotretinoin Capsules (NDA 21-951), conduct a clinical safety study with this compound as a condition of approval. Cipher submitted a proposed protocol synopsis for such a study on 1-11-08.

The Division of Epidemiology in the Office of Surveillance and Epidemiology (DEPI/OSE) has been asked to comment on the design of the proposed Phase 3 trial of the Cipher isotretinoin formulation, with respect to neuropsychiatric safety assessments.

## **2 MATERIAL REVIEWED**

The sponsor submitted a study synopsis for a Phase III study. The sponsor's synopsis states that the purpose of the study will be to evaluate the safety and efficacy of the new formulation in comparison to Accutane; however, DDDP's primary concern is assessment of the comparative safety profile. Briefly, the proposed study would be a 16-week, randomized, double-blind, parallel-group trial involving 600 patients with severe recalcitrant nodular acne. Randomized treatment groups (1:1 randomization ratio) will be either marketed isotretinoin or the Cipher formulation, at a daily dosage of 1 mg/kg/day. In addition to collection of adverse event data in the usual fashion, with clinical assessments every four weeks, the Beck Depression Inventory (BDI) will be completed by subjects at baseline and endpoint. Subjects with BDI scores  $\geq 31$  at baseline will be excluded, as will patients who are depressed, have a history of depression, have a family history of depression, or have taken antidepressant medication within the past 6 months.

## **3 DISCUSSION**

We have the following comments regarding the assessment of neuropsychiatric events in the proposed study.

1. Psychiatric assessments should be obtained at every patient contact (i.e., every 4 weeks) throughout the study, in addition to the final visit at the end of the 16 week treatment period.
2. In addition to the BDI, it would be desirable to include psychiatric assessments for conditions other than depression, since the neuropsychiatric effects of retinoids are not necessarily limited to depressed mood. In Phase 3 psoriasis trials of another retinoid compound, tazarotene, the sponsor included the following neuropsychiatric assessments: the patient self-rated Brief Symptom Inventory (BSI)<sup>2</sup>, the Mini International Neuropsychiatric Interview (MINI)<sup>3</sup> which was administered by a mental health clinician,

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<sup>1</sup> Strauss JS, Leyden JJ, Lucky AW, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: A randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol* 2001;45:196-207.

<sup>2</sup> Derogatis LR and Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychological Medicine* 13:595-605, 1983.

<sup>3</sup> Sheehan DV, Lecrubier Y, Sheehan H, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(suppl 20):22-33.

and direct questioning by clinical trial staff regarding mood and suicidal feelings at each clinical visit.<sup>4</sup>

3. For prospective assessment of suicidality, a newer instrument which might be employed is the Columbia Suicide Severity Rating Scale; the preferred instrument recommended by the Division of Psychiatry Products.<sup>5</sup>
4. Patients in the trial should receive instructions regarding when to seek help for neuropsychiatric symptoms, similar to what appears in the current MedGuide and wallet card for Accutane.
5. The proposed study design excludes patients with a past psychiatric history. While this may be protective of subjects to the extent that such patients have a higher vulnerability to neuropsychiatric adverse reactions, it of course will result in a deficit of safety data for such a patient population. Accordingly, such patients should not be excluded from a trial intended to assess neuropsychiatric effects of the drug.
6. Addition of a non-retinoid control arm such as antibiotic treatment (e.g., tetracycline, erythromycin) should be strongly considered. There would of course be issues regarding selection of a suitable patient population (i.e., identifying a group of patients for whom randomization to isotretinoin or an antibiotic would be equally acceptable from a clinical or ethical standpoint). Additionally, there would be concerns that well-known retinoid side effects would lead to unblinding. However, if these issues can be dealt with, comparison to a non-retinoid would be very advantageous in the assessment of the safety profile. A relevant example comes from a trial of malaria prophylaxis.<sup>6</sup> In this study, approximately 1000 patients were randomized to either atovaquone-proguanil or mefloquine for malaria prophylaxis while traveling. No special neuropsychiatric assessments were performed as part of the trial. Nonetheless, a statistically significant imbalance in the occurrence of depression as an adverse event was observed, with 17/483 mefloquine-treated subjects experiencing depression compared to 3/493 atovaquone-proguanil subjects.
7. Please refer to the consult from the Division of Psychiatry Products dated 1-30-2008 for additional advice on these issues.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

The value of the proposed study for the assessment of neuropsychiatric effects would be enhanced by incorporating additional neuropsychiatric assessments into the clinical trial and by addition of a non-isotretinoin comparison group.

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<sup>4</sup> Please refer to the August 17, 2005 consult from the Division of Drug Risk Evaluation [REDACTED] (b) (4) regarding the special protocol assessment for oral tazarotene [REDACTED] (b) (4)

<sup>5</sup> Available from Dr. Kelly Posner, Columbia University, posnerk@childpsych.columbia.edu

<sup>6</sup> Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: Results from a randomized, double-blind study. Clin Infect Dis 2001;133, 1015-1021.

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**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA  
CONSULT #11045**

**Consultant Reviewer:** Gregory M. Dubitsky, M.D.  
Medical Officer  
DPP HFD-130

**Consultation Requestor:** Melinda Bauerlien, M.S.  
Project Manager  
DDDDP HFD-540

**Subject:** CIP Isotretinoin Capsules

**Date Received:** January 25, 2008

**I. Background**

The Agency has requested that Cipher Pharmaceuticals, the sponsor of CIP-Isotretinoin Capsules (NDA 21-951), conduct a clinical safety study with this compound as a condition of approval. Cipher submitted a proposed protocol synopsis for such a study on 1-11-08. A meeting between the sponsor and the reviewing division, the Division of Dermatologic and Dental Drug Products (DDDDP), was scheduled for 1-28-08 to discuss the study design and any other clinical requirements necessary for approval. It is noted that a previous regulatory decision on this NDA has been the subject of a formal dispute resolution request from the sponsor.

DDDDP has requested consultation with the Division of Psychiatry Products (DPP) to: 1) review the design of the proposed study regarding the ability to ascertain differences in psychiatric adverse events between this formulation and the currently marketed Accutane formulation and 2) comment on the tools needed to permit substantive evaluation of domains such as depression and suicidality.

**II. Review of Protocol Synopsis**

This will be a multicenter, randomized, double-blind, parallel group study with an enrollment target of 700 patients with severe recalcitrant nodular acne. Among other exclusion criteria, patients will be excluded if they

are depressed or have a history of depression, including a family history of major depression in parents or siblings. Patients who have taken medication for depression or related disorders within six months of the study will also be excluded. Also, patients with a Beck Depression Inventory (BDI) score of 31 or greater at baseline will not be enrolled. In addition, patients who previously received isotretinoin in the 180 day period preceding enrollment will be excluded if that treatment was associated with severe effects, such as depression or insomnia, that affected normal daily activities or raised a concern for further isotretinoin therapy.

Patients will be randomized in a 1:1 ratio to one of two treatments: CIP-Isotretinoin Capsules at a dose of about 1 mg/kg/day given twice daily OR Accutane at a similar dose with an identical regimen. Dosing will be stratified so that patients within a given weight range will receive the same dose. The administered products will appear identical. Patients will be treated for 16 weeks. Those with a BDI score of 31 or greater at week 16 will be referred to a psychiatrist.

Post-baseline visits will occur at weeks 4, 8, 12, and 16. A post-treatment follow-up visit will also occur at week 20. Monitoring for the emergence of psychiatric signs and symptoms will be accomplished by documenting all adverse events reported by the patient or observed by the investigator during the study and self-rating on the BDI at baseline and at week 16. The primary efficacy endpoint will be the change in the total nodular lesion count (facial and truncal) at week 16. A secondary safety endpoint will be the change from baseline in the BDI score.

### **III. Conclusions and Recommendations**

Based on my review of the submitted protocol synopsis and an examination of previous DPP recommendations regarding assessment of psychiatric symptoms in clinical trials with retinoic acid products, I have the following recommendations.

- 1) The study should not exclude patients with a personal or family history of depression unless there is active depressive illness at the time of enrollment. The use of this drug would unlikely be contraindicated in such

patients and excluding these patients from the study will preclude any assessment of safety in this patient sample.

2) Use of the BDI for screening and monitoring for the emergence of significant depressive symptomatology is acceptable. However, the protocol synopsis does not specify which version of the BDI will be used. If the original instrument (BDI-I) will be utilized, the cutoff of 31 for enrollment seems to high since the most recent guidelines for interpreting scores suggest that scores of 30 or higher indicate severe illness. If this instrument will be used, a cutoff of 17 or higher, indicating moderately severe depression or worse, seems more appropriate.<sup>1</sup> The sponsor should be requested to clarify which version of the BDI will be administered and to justify the BDI criterion for screening patients and referring study participants for psychiatric evaluation.

3) The BDI will not be useful to identify psychiatric conditions other than depression at baseline. To more comprehensively evaluate study subjects with respect to other pre-existing psychiatric conditions, it is recommended that the Structured Clinical Interview for DSM-IV (SCID) be administered prior to study treatment.

4) Similarly, the BDI will not be useful for monitoring for the emergence of non-depressive psychiatric symptoms during the trials. It is recommended that an instrument such as the Brief Symptom Inventory (BSI-53) be administered at baseline and during the trial to detect the emergence of psychiatric symptoms other than those of depression. The BSI-53 is a self-report scale that rates nine domains of psychopathology, including anxiety, psychosis, and hostility. Information about this scale can be found at <http://www.pearsonassessments.com/tests/bsi.htm>. It is further recommended that protocol provide for prompt psychiatric referral of any study participant who meets one of the following BSI-based criteria: a) a 25% or greater increase from baseline in the subscore for any of the nine psychopathology domains or b) an increase of at least two points or a subscore greater than or equal to three in the depression, hostility, or psychoticism domains.

5) Additionally, it is recommended that the Columbia-Suicide Severity Rating Scale (C-SSRS) be added as a clinical assessment tool in this study to systematically evaluate the emergence and seriousness of suicidal ideation that emerges during the trial. A copy of this scale was

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<sup>1</sup> Yonkers KA and Samson J. Mood Disorder Measures in *Handbook of Psychiatric Measures*, American Psychiatric Association, Washington, DC, 2000.

sent via email from Dr. Mitch Mathis, DPP deputy Director, to Dr. Markham Luke, DDDDP Team leader, on 1-25-08. If another copy of this scale is needed, please contact the undersigned reviewer.

6) Administration of the above instruments at baseline and week 16, as proposed for the BDI, is insufficient to detect the emergence of significant psychiatric symptoms in a timely manner. It is strongly recommended that the above ratings be conducted at each visit (baseline and weeks 4, 8, 12, and 16). Furthermore, since the visits occur at only four week intervals, patients should be instructed to contact the investigator promptly if any substantial symptoms of depression, mania, suicidality, hostility, anxiety, psychosis, or cognition disturbance are experienced between visits.

Gregory M. Dubitsky, M.D.  
January 29, 2008

cc: HFD-130/Dubitsky  
/Khin  
/Laughren  
/Berman  
HFZ-540/Bauerlien

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