

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021951Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 8 , 2012
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA #	21951 IND 64, 927
Applicant	Cipher Pharmaceuticals Inc
Date of Submission	Letter date: November 29, 2011 CDER stamp date: November 29, 2011
PDUFA Goal Date	May 29, 2012
Proprietary Name / Established (USAN) names	TRADENAME/ isotretinoin
Dosage forms / Strength	Capsule – 10, 20, 30, and 40 mg
Proposed Indication(s)	Severe, recalcitrant nodular acne
Recommended:	<i>Approval</i>

1. Introduction

TRADENAME (isotretinoin) capsules, is a oral drug product for which the applicant seeks approval under Section 505 (b) (2) of the Federal Food Drug and Cosmetic Act for the treatment of severe, recalcitrant nodular acne in patients 12 of age and older. The current submission from Cipher, dated November 29, 2011, is a response to the approvable action; letter dated April 25, 2007.

This application is for a new formulation of isotretinoin, a capsule in an array of strengths (10, 20, 30, and 40 mg). The proposed dosing regimen is 0.5 to 1 mg/kg/day given in two divided doses *without regards to meals* for 15 to 20 weeks. The listed drug is Accutane[®] (isotretinoin). Accutane[®] was approved on May 7, 1982 for the treatment of severe, recalcitrant nodular acne in patients 12 of age and older. The recommended dosing regimen of Accutane[®] is 0.5 to 1 mg/kg/day given in two divided doses *with* food for 15 to 20 weeks. Failure to take Accutane[®] with food will significantly decrease absorption. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustment up to 2 mg/kg /day. Due to business considerations, Hoffmann-La Roche Inc made a decision to stop marketing Accutane[®] and requested withdrawal under 21 CFR 314.150(c) of approval of new drug application (NDA) Accutane[®] (isotretinoin) Capsules, 10, 20, and 40 mg (notice published in the Federal Register on November 22, 2010). However, four generic versions of the drug are currently available to patients.

Therapeutic benefit, Safety issues and Risk Management: Isotretinoin is uniquely effective in treating patients with severe nodular acne, a disease which can be painful and disfiguring. In many patients, the disease was cured after a 4 to 5 month course of treatment. However,

isotretinoin is highly teratogenic, contraindicated in pregnancy, and labeled as Pregnancy Category X. In order to mitigate the risks of teratogenicity and to minimize fetal exposure associated with isotretinoin, the isotretinoin sponsors in collaboration with the FDA developed a **Risk and Evaluation Mitigation Strategy (REMS)** program called **iPLEDGE** intended to prevent the use of the drug by pregnant women. iPLEDGE (initially approved by FDA under 21 CFR 314.520 - Subpart H, on August 12, 2005) is a restricted distribution program where all concerned parties including the prescribers, patients, pharmacy, and distributors must be registered and activated with the iPLEDGE program in order to dispense, prescribe, or take isotretinoin.

Isotretinoin labeling carries a boxed warning for risk of severe birth defects if pregnancy occurs while taking isotretinoin. Labeling also includes warnings for psychiatric disorders, pseudotumor cerebri, serious skin reaction, pancreatitis, lipid abnormalities, hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, and vision impairment.

Regulatory history:

- **Original application:** On Jun 27, 2005, the applicant submitted original new drug application for a new formulation of isotretinoin. This application was submitted pursuant to 505(b)(2) of the Federal Food, Drug and Cosmetic Act and proposed approval of TRADENAME (isotretinoin) capsules based upon bioequivalence comparison to the listed drug, Accutane[®]. The applicant did not conduct clinical trials to determine the safety and efficacy of their product, but only pharmacokinetic studies.
The applicant conducted a multi-dose bioequivalence trial demonstrating that under fed conditions, the TRADENAME (isotretinoin) product has a similar rate and extent of exposure as that of Accutane[®]. However, under fasted conditions, the TRADENAME (isotretinoin) product demonstrates greater bioavailability (approximately 2 fold higher bioavailability compared to the listed drug). The above data suggested a high probability of more exposure to isotretinoin for the patient. Additionally, it was noted that during the bioequivalence trial 7 neuropsychiatric events were reported, 6 in TRADENAME (isotretinoin) group and only one in the Accutane[®] group. A total of 3 discontinuations occurred because of neuropsychiatric events, all on the TRADENAME (isotretinoin) group. Therefore, because no clinical trials were performed, the effect of this bioinequivalence of the TRADENAME (isotretinoin) product to Accutane[®], in terms of safety was unknown.
- **Approvable action:** An approvable letter was sent to the applicant on May 1, 2006. The approvable letter cited, among other deficiencies, the increased bioavailability of TRADENAME (isotretinoin) compared to the listed drug, Accutane[®], precluding the reliance on the Agency's previous finding of safety and effectiveness for Accutane[®] as the sole basis of approval for TRADENAME (isotretinoin) capsules.
To address this deficiency, the Agency recommended that the applicant conduct a clinical safety and efficacy trial or a population PK trial comparing TRADENAME (isotretinoin) capsules to Accutane[®] at a dose of 1.0 mg/kg/day.

- **Complete Response:** The applicant submitted a complete response to the original approvable letter on October 26, 2006. However, this application only addressed one deficiency outlined in the action letter, dose proportionality across its different dosage forms.
- **Second approvable action:** A second approvable letter was sent to the applicant on April 25, 2007. The letter cited a chemistry deficiency and the lack of an adequate basis to rely on the finding of safety for the listed drug. Again, the applicant was advised to conduct a clinical trial to demonstrate the safety of their drug product in comparison to the listed drug.
- **SPA:** On February 11, 2009, the applicant submitted revised protocol for a Phase 3 trial (ISOCT.08.01): “*A Double-Blind, Randomized, Phase III, Parallel Group Study Comparing the Efficacy and Safety of CIP-Isotretinoin to the Marketed Formulation of Isotretinoin in Patient with Severe Recalcitrant Nodular Acne*” (based on extensive discussion between Cipher and FDA during Guidance meetings held on August 6, 2008, September 24, 2008, September 29, 2008, and January 7, 2009, with regard to clinical study design, safety and efficacy assessment); Letter dated April 8, 2009.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

The current submission from Cipher, dated November 29, 2011, is a response to the approvable action; letter dated April 25, 2007.

The following issues were articulated in the **Complete Response** letter (April 25, 2007):

Clinical

1. The application did not establish an adequate basis for the Agency to rely on our previous finding of safety for the listed drug, Accutane[®]. You have not demonstrated that the difference in the pharmacokinetic profile of CIP-Isotretinoin as compared to Accutane[®] is not clinically meaningful with regard to the safety profile of CIP-Isotretinoin. Specifically, the information provided in the application demonstrates that your product is not bioequivalent to the listed drug. Your product will occupy the upper range of exposures expected with the listed drug due to the lower absorption of Accutane[®] under fasted conditions. Given that real world use of Accutane[®] likely includes exposure under fasted conditions, it is reasonable to assume that Accutane[®] users experience a range of exposures that are lower than anticipated for your product, and that these lower exposures could mitigate against dose-related toxicities.

Our understanding of the safety profile of Accutane[®] is based on the original clinical trials and more than two decades of post-marketing safety information. Significant safety information related to isotretinoin has emerged during the post-marketing period, including

concerns about systemic toxicities and potential neuro-psychiatric events. The isotretinoin exposures with your product are anticipated to lie more consistently in the upper range of exposures seen with Accutane[®] and may result in a safety profile that differs from the listed drug. Thus, your claim of no difference in terms of safety between CIP-Isotretinoin and the listed drug (Accutane[®]) cannot be supported without clinical trial data comparing your product to the listed drug, Accutane[®].

To address this deficiency, we recommend that you conduct a clinical trial in patients with severe, recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane[®] at a dose of 1.0 mg/kg/day. This trial should have a sufficient number of patients to detect adverse events which occur at an incidence of 1% in the treated population. Adequate monitoring and evaluation of adverse events of particular concern with exposure to isotretinoin should be fully considered in the study design. These include, but are not limited to, prospective assessment for psychiatric and CNS events, adequate monitoring for bone mineral density changes, adequate testing for hearing and vision impairment, and thorough follow-up of all patients with abnormal laboratory tests.

You are strongly encouraged to obtain agency advice concerning the conduct and design of this clinical trial prior to implementation.

Chemistry, Manufacturing and Controls

2. The proposed dosage form is considered to be an (b) (4) capsule. Therefore, the dissolution test should be established with multiple time points (30, 60, 120, and 240 minutes) with respective acceptance criteria.

3. CMC/Device

Drug substance: The drug substance is isotretinoin. Chemically, isotretinoin is a retinoid drug and its molecular weight is 300.44 g/mole.

The specification for the isotretinoin drug substance is found acceptable.

The analytical methods were reviewed and found adequate to assure the identity, strength, quality and purity the drug substance.

Drug Product: TRADENAME (isotretinoin) capsule consists of hard gelatin capsule (b) (4) with mixture of excipients (b) (4), soybean oil, sorbitan monooleate and propyl gallate. (b) (4)
The TRADENAME (isotretinoin) capsule will be made in 10mg, 20mg, 30mg and 40mg strengths. The table below lists the quantitative composition of all four strengths.

Table 1: Composition of TRADENAME (isotretinoin) Capsule

Ingredient and Test Standard	Amount per capsule (mg) Strength 10 mg	Amount per capsule (mg) Strength 20 mg	Amount per capsule (mg) Strength 30 mg	Amount per capsule (mg) Strength 40 mg	Function
Isotretinoin, USP	10	20	30	40	Active
Stearoyl Macroglycerides	(b) (4)				
(b) (4)					
Soybean Oil, USP					
Sorbitan Monooleate, NF (SPAN 80)					
Propyl Gallate, NF					
(b) (4)					

Satisfactory 36-months real-time stability data were provided for 10mg, 20mg and 30mg batches. Based on the current specification (including the tentative dissolution test), it is concluded that the drug products will remain stable during the proposed expiration dating period. Therefore, 36 month of the expiration dating period is granted for these strengths. However, a single batch of 40mg capsules has only 22 months of the long term stability data and its stability study is ongoing. Based on available data, 24-months of expiration dating period can be given to the 40mg strength capsules.

TRADENAME (isotretinoin) Capsules 10, 20, 30 and 40mg capsules will be packaged in blister sheets of 10 capsules, which will be then packaged in (b) (4) boxes. Capsules were made of (b) (4) hard gelatin (b) (4) in order to protect from light. Stability data on the drug product support the adequacy of this container/closure system.

Recommendation and Conclusion on Approvability

- The applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.
- Approval of NDA 21951 pending agreement of the applicant with the recommended labeling/label revisions and “Acceptable” recommendation from the Office of Compliance regarding facilities inspections.

The reader is referred to the comprehensive review by Tarun Metha, Ph.D (Division of New Drug Quality Assessment II; Branch IV; dated 04/12/07 and 04/18/12).

ONDQA- Biopharmaceutics Team reviewed the acceptability of the proposed dissolution method and acceptance criterion for quality control, and provided a recommendation on the most appropriate classification for the proposed drug product.

Based on submitted data the Biopharmaceutics Team made the following conclusion and recommendations:

- Drug product dosage form classification:

(b) (4)
(b) (4) an immediate-release (IR) classification is recommended for TRADENAME (isotretinoin) Capsules.

- Dissolution Acceptance Criteria

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. The dissolution method needs to be improved to reduce variability associated with inefficiencies in capsule disruption, the amount of surfactant and the amount of enzyme used. The goal of an optimal quality control dissolution method is to achieve reproducible product profiles. Therefore, the applicant should conduct “Dissolution method development study” with objective to optimize the current dissolution test method and acceptance criteria for improved quality assurance of batch to batch consistency.

The applicant and the Agency have come to an agreement concerning the dissolution acceptance criteria for the different strengths of TRADENAME (isotretinoin) capsules. The following dissolution method and acceptance criteria are acceptable for approval on an interim basis for release and stability.

(b) (4)

- **Recommended Post Marketing Commitment:**

PMC #1 Description: Dissolution method development study

Conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

FDA will make a decision on the final dissolution method for your isotretinoin capsules after reviewing your dissolution method report. Once an agreement is reached on the final test method, use the final test method to propose final dissolution acceptance criteria for your isotretinoin capsules. Your proposal should be supported by dissolution data from at least the first three (3) validation lots of each capsule strength, and two (2) additional commercial batches of each strength. If the dissolution report provides for a new faster-release dissolution method (i.e., complete release/dissolution for all the strengths in < 90 minutes) and the provided data support the approval of this method, you may propose the implementation of a single-point dissolution criterion. Otherwise, implement at least a two-point criteria, with the first time point being a range of appropriate variability (ideally +/- 10%).

From the perspective of Biopharmaceutics, NDA 21-951 for TRADENAME (isotretinoin) capsules is recommended for approval with a Post Marketing Commitment.

The reader is referred to the comprehensive review by Minerva Hughes, Ph.D.; Biopharmaceutics Reviewer; Office of New Drug Quality Assessment dated 04/16/12 and 05/07/12.

4. Nonclinical Pharmacology/Toxicology

The applicant has not conducted any nonclinical studies with the drug substance/product. No nonclinical studies have been submitted within this NDA.

The applicant seeks approval of their application under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. This NDA relies on published data for isotretinoin as well as the Agency's findings of safety and efficacy for the listed drug Accutane[®] [(isotretinoin) NDA

18622]. The adequate clinical bridge (which consists of relative bioavailability trials) has been established [TRADENAME (isotretinoin) is bioequivalent to Accutane[®] under fed conditions, and fed conditions is the highest level attained], as discussed in section 5 of this review. Therefore, labeling for TRADENAME (isotretinoin) Capsules, Section 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility, will have the same information as the labeling for the listed drug.

The reader is referred to the comprehensive review by Dr. Jiaqin Yao for a full discussion of the nonclinical pharmacology/toxicology data (dated 04/10/12). Drs. Yao and Hill did not recommend further nonclinical studies or Phase 4 commitments/requirements, and recommended an *Approval* action from a pharmacological/toxicological perspective.

5. Clinical Pharmacology

This application pursued a 505(b)(2) pathway for TRADENAME (isotretinoin) Capsules and identified Accutane[®] as the listed drug. To support this application, with the original application, the applicant conducted relative bioavailability (BA) trials with their product and the listed drug (Accutane[®]) under fasting and fed conditions and a food effect study. In addition, the applicant conducted studies to demonstrate proportionality between different strengths under fasting and fed conditions to support interchangeability among different strengths, and single and multiple dose PK estimations obtained by serial blood sampling. These studies were reviewed by Dr. Dennis Bashaw (dated 04/21/2006; 04/09/2007). The results of relative BA trials showed that under fed conditions TRADENAME (isotretinoin) was bioequivalent (BE) with Accutane[®], but they were not BE under fasting conditions. Specifically, the exposure of TRADENAME (isotretinoin) was approximately 2 fold higher than Accutane[®] when both the formulations were administered under fasting conditions. The relative BA trial was conducted using only the 20 mg strength of TRADENAME (isotretinoin), but results of proportionality studies support application of these findings to other strengths. The results of proportionality trials indicated that the BA of TRADENAME (isotretinoin) increased in a proportional manner between 10 mg and 30 mg strength under both fasting and fed conditions.

The results of the food effect trial (using 30 mg strength), indicated that the effect of food was substantially larger on the Accutane[®] formulation compared to the TRADENAME (isotretinoin); however, there was still a significant food effect on the TRADENAME (isotretinoin). In the presence of food, the systemic exposure (AUC) increased on average 1.5 times for TRADENAME (isotretinoin) formulation and approximately 2.5 times for the Accutane[®] formulation. The peak exposure (C_{max}) to isotretinoin increased under fed conditions and was approximately 1.6 times and 2.7 times for TRADENAME (isotretinoin) and Accutane[®] formulations, respectively, compared to fasting conditions. It should be noted that per Accutane[®] labeling drug “should be administered with a meal”. However, the applicant is proposing to label their drug product to be administered without regards to meals.

With the original submission, the applicant was seeking approval of 3 strengths of the TRADENAME (isotretinoin) capsules, 10 mg, 20 mg and 30 mg. However, in this

resubmission the applicant has requested to market an additional strength of TRADENAME (isotretinoin) capsule, 40 mg.

The applicant conducted 3 new Clinical Pharmacology trials:

- ISOPK.08.02 – Effect of food on the 40 mg strength (14 subjects)
- ISOPK.09.01 – Relative BA study of 2 x 20 mg TRADENAME (isotretinoin) vs. 1 x 40 mg TRADENAME (isotretinoin) under **Fed** conditions (49 subjects)
- ISOPK.09.02 – Relative BA study of 2 x 20 mg TRADENAME (isotretinoin) vs. 1 x 40 mg TRADENAME (isotretinoin) under **Fasting** conditions (50 subjects)

ISOPK.08.02 – Effect of food on the 40 mg strength

The effect of food on PK of the new 40 mg strength appears to be similar with that observed with previously evaluated 30 mg strength: AUC and C_{max} under fed conditions was approximately 1.5 and 1.3 fold respectively, higher with food compared to fasting.

SOPK.09.01 – Relative BA study of 2 x 20 mg TRADENAME (isotretinoin) vs. 1 x 40 mg TRADENAME (isotretinoin) under Fed conditions

The exposure of 2 x 20 mg and 1 x 40 mg were BE with the 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C_{max} within the no effect boundary of 80% to 125%. This indicates that the PK of isotretinoin increased in a proportional manner between 20 mg to 40 mg strengths under Fed conditions. Therefore, based on previous results (proportionality between 10 mg to 30 mg strength under both fasting and fed conditions) and these results under fed conditions the 4 strengths (10 mg, 20 mg, 30 mg and 40 mg) could be used interchangeably.

ISOPK.09.02 – Relative BA study of 2 x 20 mg TRADENAME (isotretinoin) vs. 1 x 40 mg TRADENAME (isotretinoin) under Fasting conditions

The exposure of 1 x 40 mg strength was slightly lower than 2 x 20 mg strength. Specifically the AUC and C_{max} with 1 x 40 mg strength were approximately 15% and 20%, respectively, lower than those following administration of 2 x 20 mg strength. However, this slightly less than proportional increase in exposure with the 40 mg strength of TRADENAME (isotretinoin) under fasting conditions is expected to have minimal effect on drug efficacy based on the observed magnitude of food effect between TRADENAME (isotretinoin) and Accutane[®]. [The TRADENAME (isotretinoin) systemic exposure under fasting conditions lie in between Accutane[®] fasting and TRADENAME (isotretinoin) and Accutane[®] fed. Specifically, the TRADENAME (isotretinoin) exposure under fasting conditions were approximately 2 fold higher than Accutane[®] fasting]

Base on the results from the above trials, Dr Shukla concluded that the TRADENAME (isotretinoin) capsule could be administered without regards to meals; which will be included in the labeling (Section 2 DOSAGE AND ADMINISTRATION).

In the Phase 3 trial ISOCT.08.01 population PK parameters were evaluated by the Pharmacometrics reviewer Dr. Dhananjay Marathe. According to Dr. Marathe, no difference in exposures between the two formulations under study usage was observed (where most doses were taken with the food but some taken after fasting). The mean isotretinoin exposure in

pediatric subjects (age range 12 – 17 years) was slightly lower than in adults [the exposures in pediatric subjects were 9.3% and 6.0% lesser than adults for the Reference Product and TRADENAME (isotretinoin) respectively]. No dose adjustment is recommended for pediatric patients.

The applicant has not conducted any drug-drug interaction trials. The labeling for TRADENAME (isotretinoin) Capsules “*Drug Interactions*” section (Section 7) should be identical to the listed drug labeling.

The reader is referred to the comprehensive review by Chinmay Shukla, Ph.D. and Dhananjay D. Marathe, Ph.D. for a full discussion of the clinical pharmacology data (dated 04/12/12).

The clinical pharmacology review team recommended *Approval* of this application.

Labeling Recommendations (The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion); only major changes

2.1 Recommended Dosage

Recommended dosage range for **Trade name** ^{(b) (4)} -is ^{(b) (4)} **0.5 to 1 mg/kg/day given in two divided doses** without regard to meals **for 15 to 20 weeks (see Table 1). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid. [see *Information for Patients* (17.1)].**

The safety of once daily dosing with **Trade name** ^{(b) (4)} has not been established. Once daily dosing is not recommended.



6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant has established a biobridge between their product and listed drug in order to rely upon the Agency's finding of effectiveness for Accutane[®] (see Section 5 of this review). In addition, the applicant submitted data from one pivotal trial, Study ISOCT.08.01, to compare the safety (and supportive evidence for effectiveness) of their product taken orally twice daily for 20 weeks in the treatment of severe recalcitrant nodular acne to a currently marketed isotretinoin product (Reference Product). The trial was multi-center, prospective, randomized, active-controlled, parallel group study. This trial was a non-inferiority trial comparing TRADENAME (isotretinoin) to a Reference Product. The general trial design, the co-primary endpoints, analysis population, statistical analysis methods and primary method of handling missing data were in agreement with the Agency's comments per the special protocol agreement letter dated 4/8/2009.

Subjects determined to be eligible during the screening phase were randomized to 2 treatment groups, TRADENAME (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 orally with meals for the first 4 weeks, followed by approximately 1 mg/kg/day divided into two doses taken with meals (breakfast and dinner) for 16 weeks. Efficacy and safety evaluations were assessed at baseline, Week 2, Week 4, Week 8, Week 12, Week 16, and Week 20 with a follow up visit at Week 24.

A total of 925 subjects were randomized in the trial, 464 on TRADENAME (isotretinoin) and 461 on referenced product.

The population enrolled was subjects 12 years of age and older with severe recalcitrant nodular acne, with at least 10 nodules at baseline. Slightly less than half of the subjects had ≥ 14 nodules at baseline in both arms and had a mean of 29 inflammatory lesions in both arms. The majority of subjects (70%) had a Physician's Global Severity Assessment (PGSA) baseline score of 4 (severe).

Forty three percent (43%) of the enrolled subject were less than 18 years of age. Approximately 60% of subjects in both arms were male, predominately white (87%) and non-Hispanic (87%). The two treatment groups were similar with respect to demographic and baseline characteristics.

A total of 813 (87.9%) subjects completed the treatment phase (20 weeks) of the trial and 795 (85.9%) subjects completed the follow-up phase (4 weeks). Overall 130 (14.1%) subjects discontinued from the trial, 70 (15.1%) from the TRADENAME (isotretinoin) group and 60 (13.0%) from the Reference Product group. In both treatment groups, the most frequent reason for discontinuation was that the subject was lost to follow-up. Thirty four (3.7%) subjects discontinued due to one or more AEs, 19 (4.1%) in the TRADENAME (isotretinoin) group and 15 (3.3%) in the Reference Product group.

The co-primary endpoints are defined as (i) change from Baseline to Week 20 in the total nodular lesion count, and (ii) success rate with success defined as at least 90% clearance in the total number of nodular lesions.

TRADENAME (isotretinoin) was considered non-inferior to the Reference Product if both of the following criteria are met: (1) the upper bound of the 2-sided 95% confidence interval (CI) of mean difference was less than or equal to 4 for change in total nodular lesion count; 2) the lower bound of the 2-sided 95% CI of difference in success rate was greater than or equal to (b) (4). The 95% confidence limit of the mean difference in the total nodular lesion counts [TRADENAME (isotretinoin) minus Reference Product] was estimated by the analysis of covariance (ANCOVA) model with treatment, analysis site, gender and baseline lesion counts as covariates. The 95% confidence limit of difference [TRADENAME (isotretinoin) minus Reference Product] in proportions of subjects who achieved at least a 90% reduction in the total nodular lesion count was estimated under the normal approximation.

The analysis for the co-primary endpoints was based on both intent-to-treat (ITT) population and per-protocol (PP) population. The ITT population is defined as all subjects who were randomized and received the study medication. The PP population is defined as all randomized subjects who were at least 80% compliant with their assigned treatment with no major protocol violations.

The results for both co-primary endpoints along with the baseline disease severity are presented in Table 2.

Table 2: Analysis Results for the Co-Primary Endpoints ITT and PP Populations

	TRADENAME (isotretinoin)	Reference Product	95% CI of Difference
Baseline lesion count. Mean (SD)	18.4 (14.7)	17.7 (10.8)	N/A
Change in lesion count. Mean (SD)			
ITT (LOCF)	-15.68 (14.02)	-15.62 (10.59)	(-0.233, 1.205)
PP	-17.01 (14.26)	-16.52 (10.57)	(-0.271, 0.548)
Success Rate^a			
ITT (LOCF)	324/464 (69.8%)	344/461(74.6%)	((b) (4), 0.97%)
PP	286/363 (78.8%)	292/361 (80.9%)	(-7.94%, 3.74%)

^aSuccess is defined as at least 90% reduction from Baseline to Week 20 in the total number of nodular lesions.
 Source: NDA 21-951: Statistical Review by Yuqing Tang, PhD Division of Biometrics 3: table 6, page 11, in DARRTS 4/4/12.

For the ITT population with missing data imputed using last observation carried forward (LOCF), the non-inferiority criterion for absolute change in total nodular lesion count was met. The trial missed the non-inferiority criterion (-10%) for proportion of subjects with at least 90% clearance (95% CI = (b) (4) 0.97%). For all subjects who completed the trial, the non-inferiority margin of at least 10% was met. The non-inferiority criteria for both co-primary endpoints were met for the PP population.

Secondary Endpoints: Treatment success at Week 20, defined as a grade of either 0 (clear) or 1 (almost clear) on the 6-point Physician's Global Severity Assessment (PGSA) scale was assessed as a secondary outcome, along with a non-inferiority margin of 10%. However, the applicant did not specify the PGSA score as one of the inclusion criteria. Descriptively, there were 326 out of 464 (70%) subjects for the TRADENAME (isotretinoin) arm and 351 out of 461 (76%) subjects for the reference product that had a PGSA score of "Clear" (0) or "Almost Clear" (1) at Week 20 based on the ITT population.

The reader is referred to the reviews of Dr. Yuqing Tang (dated 04/04/12) and Dr. Denise Cook (dated 04/23/12) for a more complete discussion of the efficacy results. I concur with the conclusions of the clinical and statistical reviewers, Dr. Denise Cook and Dr. Yuqing Tang, respectively, that the data support a determination of efficacy; both Dr. Cook and Dr. Tang recommended *Approval* of the application.

8. Safety

To address the first deficiency (articulated in the Complete Response letter dated April 25, 2007), the applicant submitted data from one pivotal trial, Study ISOCT.08.01 to compare the safety of their product taken orally twice daily for 20 weeks in the treatment of severe

recalcitrant nodular acne to a Reference Product (currently marketed generic isotretinoin; as the listed drug is no longer marketed).

The safety population consisted of 924 subjects, 464 on TRADENAME (isotretinoin) and 460 on Referenced Product. Enrolled subjects were between the ages of 12 and 52 years, with 43% of the enrolled subjects < 18 years old. Approximately 60% of subjects in both arms were male; predominately white (87%). 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). Eighty seven percent (87.3%) received at least 19 weeks of treatment.

During the trial, 130/924 (14%) subjects discontinued treatment. In the TRADENAME (isotretinoin) group, 19 (4%) were due to AE, and 15 (3%) were from the Referenced Product group. The most common AE that lead to discontinuation for the TRADENAME (isotretinoin) group was psychiatric (5) and GI (5); and for the Referenced Product group it was psychiatric (5), musculoskeletal and connective tissue disorders (4). There were no deaths during and for 30 days after the trial (which was the follow-up period). There were 12 serious adverse events (SAEs) during the course of the trial, 7 (1.5%) in the TRADENAME (isotretinoin) group and 5 (1.1%) in the Referenced Product group. Three of the SAEs in the TRADENAME (isotretinoin) group were considered possibly related to study product (abdominal pain (2) and migraine). All subjects recovered without sequelae. None of the SAEs in the Referenced Product group was considered related to study medication.

The majority of subjects in both arms experienced an adverse event, 92% in the TRADENAME (isotretinoin) arm and 90% in the Reference Product arm. The majority of subjects experienced mild AEs [55% vs. 53% in the TRADENAME (isotretinoin) and Reference Product groups, respectively], or moderate AEs (33% vs. 32% in the two groups, respectively), whereas severe AEs only occurred in 20 (4%) of patients in the TRADENAME (isotretinoin) and 21 (5%) of patients in the Reference Product group. The most common AEs were dry lip and dry skin (reported by ~ 45% in both arms) followed by back pain (reported by 20% in both arms) and dry eye [reported by 19% in the TRADENAME (isotretinoin) and 17% in the Reference Product group]. Other AE reported in ≥5% of subjects (in both arms) were: arthralgia, epistaxis, headache, nasopharyngitis, chapped lips, dermatitis, blood CK increased, chelitis, musculoskeletal discomfort, upper respiratory tract infection and visual acuity reduced.

Neuropsychiatric Evaluation

In this trial, psychiatric assessment was performed using the following 4 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.
- 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.

All subjects had baseline psychiatric evaluations. In the TRADENAME (isotretinoin) arm 11.6% of patients had a history of psychiatric disorder compared to 13.9% in the Reference Product arm. Ten subjects, 5 in each group withdrew from the trial due to psychiatric events. Psychiatric adverse reactions were reported in 6.3% (29/464) of subjects in the TRADENAME (isotretinoin) arm and 5.9% (27/460) of subjects in the Reference Product arm. Insomnia and anxiety was reported in > 1% of subjects, [3% and 2% for TRADENAME (isotretinoin) and RP, respectively, for the former and 1% and 1.5%, respectively for the latter]. There was no difference in the incidence of depression in the two groups, 3 (0.6%) for the TRADENAME (isotretinoin) group and 4 (0.9%) for the Reference Product group.

Using the **PHQ-8**, 4 subjects on TRADENAME (isotretinoin) and 5 subjects on Reference Product met the threshold with a score of 10 for clinically significant depression. A total of 11 subjects on the **C-SSRS** at some point post-baseline reported suicidal ideation, 4 in the TRADENAME (isotretinoin) arm and 7 in the Reference Product arm. There was no imbalance between the drug products in terms of level of suicidal ideation, with the lowest level of severity (wish to be dead) most common in both arms. Using the **GAD-7**, the clinically significant threshold for anxiety was met by 2 subjects in the TRADENAME (isotretinoin) arm and 4 subjects in the Reference Product arm. For the **psychosis assessment**, only 1 subject in each group responded to at least 1 of 3 psychosis assessment questions in the affirmative. Both subjects received pharmacotherapy.

In summary, the psychiatric assessments performed in study ISOCT.08.01 appear to be adequate and are consistent with recommendations provided by Division of Psychiatry Products (DPP) and the Agency's comments per the special protocol agreement letter dated 4/8/2009. The trial ISOCT.08.01, which compared the two drug products at 1.0 mg/kg /day over 20 weeks of therapy, did not demonstrate any significant difference in terms of neuropsychiatric events. Therefore, labeling (relevant sections) for the TRADENAME (isotretinoin) capsules will be the same as for the listed drug.

The reader is referred to the reviews of Dr. Gregory M. Dubitsky (Division of Psychiatry Products; dated 02/27/12) and Dr. Denise Cook (dated 04/23/12) for a more complete discussion.

Bone Metabolism Evaluation

In the trial ISOCT.08.01 all adolescent (396; age 12-17 y/o) subjects and a subset of adult (80; age 18-54 y/o) subjects had safety evaluations (screening and monitoring) for bone metabolism (bone substudy). Bone Mineral Density (BMD) measurement in both adolescents and adults consisted of dual x-ray absorptiometry (DXA) of Anterior-Posterior (AP) lumbar spine and left hip. The initial protocol specified that adolescents would also undergo Lumbar

Spine and Total Body Less Head (TBLH) scan, however because this type of scan was unavailable at most study sites, it was deleted from the protocol. In addition to BMD, the trial included assessments of adolescents' bone age, Tanner stage of pubertal maturity (by self-assessment) and age of menarche (girls).

The baseline DXA was conducted between screening (within 45 days of baseline) and baseline. The end of treatment (EOT) scan was conducted at week 20 ± 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). Most of these adolescents underwent a third, short-term follow-up scan within 4 months after end of treatment. 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.

Adolescents:

The majority of the adolescent subjects were in the categories of white (96%), male (80%), and Tanner stages 4-5. The mean age was 15.4 years for males and 15.2 years for females. As specified in the protocol, all 396 adolescent subjects underwent DXA scans at baseline. Baseline BMD Z-scores were on average ~ 0.5 SD above subjects' peer groups, reflecting their general good health. EOT (week-20) DXA scans were conducted on 156 out of 204 subjects (76.5%) assigned to TRADENAME (isotretinoin), and 150 out of 192 subjects (78.1%) assigned to control.

Both treatment arms showed moderate increase [1.56% TRADENAME (isotretinoin), 2.04% Reference Product] 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%). 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. This appears 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. Z-score declines at the hip and femoral neck were significantly greater in boys than in girls; in part this may be because normal BMD accrual subsides in girls about 1-2 years before boys. In addition, oral contraceptive use also may have partially mitigated negative effects in girls. BMD results were somewhat more favorable in the control arm relative to TRADENAME (isotretinoin) at each skeletal site, but without statistical difference.

Overall, there were 9% (27/306) adolescent subjects who exhibited $> 4\text{-}5\%$ bone loss during the trial, mostly at total hip and/or femoral neck (2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck). The short-term follow-up DXA scans performed in this trial (up to 4 months post-treatment) showed no evidence of a trend toward BMD recovery in these subjects. 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 (3 out of 7 subjects had total hip and femoral neck BMD below pre-treatment baseline, and 2 others did not show the increase in BMD above

baseline expected in this adolescent population). The data are inadequate to conclude that subjects with BMD loss related to isotretinoin will experience recovery from this effect; this should be noted in the TRADENAME (isotretinoin) labeling (Section 8 USE IN SPECIFIC POPULATION; 8.4 Pediatric Use).

Bone age: Of the 396 adolescent subjects, 289 [146 TRADENAME (isotretinoin), 143 control] underwent left wrist/hand X-rays at both baseline and EOT. Seventeen subjects [9 TRADENAME (isotretinoin), 8 control] had an increase in bone age of at least 1.5 standard deviations. Of these 17 subjects, 13 also exhibited closure of the distal radial epiphysis. The two isotretinoin products did not appear to differ in this respect.

Adults:

Out of 529 adult (18-54 years of age) subjects in the overall study, 80 agreed to participate in the bone substudy and underwent baseline DXA scans. Thirty of the 41 subjects assigned to TRADENAME (isotretinoin) also had an EOT scan (73.2%), and 28 of the 39 subjects assigned to control also had an EOT scan (71.8%). The majority (70%) were less than 30 years of age [white (85%); female (60%)].

The BMD data from the adults in this trial are 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 years of age had 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 adult subjects 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 adult subjects were not expected to show major gains in BMD, unlike adolescents.

Musculoskeletal evaluation:

During the trial, 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. Back pain was reported by 20% of subjects. Of the 27 subjects who had significant bone loss at one or more skeletal sites on DXA, 4 subjects reported back pain during the trial (reported as “mild” and resolved before trial end). The only other musculoskeletal AEs in this group of 27 subjects were arthralgia/R knee pain (1) and joint sprain/sprained R ankle (1).

In summary, the data relevant to bone metabolism from the trial ISOCT.08.01 are consistent with previous findings for listed drug and no significant differences between TRADENAME (isotretinoin) and generic isotretinoin (Reference Product) was observed. Therefore, information from relevant sections of the approved isotretinoin product labeling should be incorporated into the TRADENAME (isotretinoin) labeling (Section 8 USE IN SPECIFIC POPULATION; 8.4 Pediatric Use; Section 5 WARNINGS AND PRECAUTIONS; 17 PATIENT COUNSELING INFORMATION; Medication Guide).

The reader is referred to the reviews of Dr. Stephen R Voss (DURP; dated 04/10/12) and Dr. Denise Cook (dated 04/23/12) for a more complete discussion.

Audiology Evaluation

Hearing safety evaluation was performed in ~ 20% of subjects participating in this trial at 10/49 centers in the United States and Canada [86 subjects in TRADENAME (isotretinoin) group and 94 subjects in the Reference Product group].

Adverse events related to the ear and labyrinth were reported in approximately 2% of the patients in each treatment group, and only a small number of patients experienced a significant threshold shift during the study period [2/86 subjects in TRADENAME (isotretinoin) group and 5/94 subjects in the Reference Product group]. The most common AE was ear pain (reported by 3 subjects in each group) and hypoacusis [reported by 3 subjects in TRADENAME (isotretinoin) group and 2 subjects in Reference Product group]. Tinnitus was reported by one subject in TRADENAME (isotretinoin) group.

Dr Kane concluded that “Overall, significant differences were not observed between the two study groups regarding changes in hearing sensitivity, subjective tinnitus or vestibular functionality.”

Therefore, labeling for TRADENAME (isotretinoin) Capsules will have the same information (for the relevant Section) as the listed drug.

The reader is referred to the reviews of Dr. by James Kane (CDRH; dated 02/28/12) and Dr. Denise Cook (dated 04/23/12) for a more complete discussion.

Ophthalmology Evaluation

Subjects were tested for visual acuity changes (on the Snellen Eye Chart) over time during each visit of the trial up to and including week 24. No significant differences between the two treatment groups were observed. Overall, 20 (4.3%) subjects in the TRADENAME (isotretinoin) arm experienced a reduction in visual acuity compared to 25 (5.4%) in the Reference Product arm.

Ten subjects (10/464; 2%) in the TRADENAME (isotretinoin) group and 4 subjects (4/460; 1%) in the Reference Product group reported having night blindness.

The most common reported AE, reported by 20% of subjects in each treatment group was dry eye.

In summary, Dr Boyd concluded that “As designed and conducted, this protocol did not provide adequate ocular monitoring of study subjects; ... Although flawed, 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.”

Recommendation from DTOP Team:

“Because this protocol did not provide adequate ocular monitoring of study subjects, the ocular safety of the study treatments was 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.”

The reader is referred to the reviews of Dr. William Boyd (DTOP; dated 02/21/12 and 04/09/12) and Dr. Denise Cook (dated 04/23/12) for a more complete discussion.

Laboratory Findings

The most frequently reported abnormalities in both treatment groups were elevated CK levels, with marked elevation (flagged by the reporting laboratory; $CK \geq 350$ U/L) being reported for 24% of subjects in the TRADENAME (isotretinoin) group and 23% of subjects in the Reference Product group. Elevated liver function enzymes (ALT, AST, and GGT) were also reported with high frequency as were increases in serum triglycerides. High alert laboratory values for ALT/AST were reported in 1.1% in the TRADENAME (isotretinoin) group and in 1.7% in the Reference Product group. Almost all subjects have some increase in the levels of triglycerides, LDL cholesterol, and total cholesterol and a decrease in the HDL cholesterol from their own baseline. Approximately half of these subjects return to their own baseline by the end of the trial (4 weeks post treatment). There is basically no difference between TRADENAME (isotretinoin) and Reference Product in the effect on lipid metabolism. In the differential white blood cell count, mean increases in the percent lymphocytes and monocytes and mean decreases in the percent neutrophils were observed over the course of the trial in both groups.

Analysis of the laboratory data did not reveal any significant differences between TRADENAME (isotretinoin) and the Reference Product. These findings are consistent with current isotretinoin (Reference Product) labeling.

Vital Signs:

There were no notable changes to the mean values for systolic and diastolic blood pressure, hear rate, and body weight in either treatment group. None of the changes in vital signs reported in individual patients were reported as AEs.

Pregnancies:

There were 2 pregnancies in the clinical trial, one in the TRADENAME (isotretinoin) arm (23 years old) and one (19 years old) in the Reference Product arm. Both subjects were using two forms of contraception [oral contraception (orthotricyclen; Loestrin 24) and male condom], and were counseled regarding contraception as per protocol. Both subjects voluntarily elected termination of the pregnancy.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held.

10. Pediatrics

The proposed indication, like for the listed drug, is “treatment of severe recalcitrant nodular acne in patient 12 years of age and older”. Because this is a 505(2)(b) application that relies for approval on the Agency’s finding of safety and effectiveness for a listed drug, Accutane[®] (the applicant has established that such reliance is scientifically appropriate), and the applicant conducted a Phase 3 trial in subjects 12 years of age and older (the relevant population for acne vulgaris and the population for whom the applicant seeks labeling), no additional pediatric trials are required.

Additionally, the Pediatric Research Equity Act (PREA) does not apply to this application because the proposed indication, active ingredient, dosage form, dosing regimen and route administration are the same as for the listed drug.

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The proprietary name has not been established. The product is referred to as TRADENAME (isotretinoin) Capsule, in this review.

The applicant submitted proposed labeling in the format that complies with the Physicians’ Labeling Rule. Professional and patient labeling were reviewed (by multidisciplinary review team), and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include (The underlined text indicates insertion recommended by the reviewer and the ~~striketrough~~ text indicates recommended deletion):

- **Boxed Warning**
 - Birth defects which have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion and premature births have been reported.
 - Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia; facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

- If pregnancy does occur during the treatment of a female patient who is taking TRADENAME, TRADENAME must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.
 - Special Prescribing Requirements
Because of the risk of teratogenicity and to minimize fetal exposure, TRADENAME is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called iPLEDGE™. Under the Trade name REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program [see Warnings and Precautions 5.2].
- **Section 5 WARNINGS AND PRECAUTIONS**
5.2 iPLEDGE Program

5.12 Skeletal

Bone Mineral Density Changes

Isotretinoin may have a negative effect on bone mineral density (BMD) in some patients. In a clinical trial of TRADENAME, 27/306 (8.8%) of adolescents had BMD declines of $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral neck, during the 20 week treatment period. Follow-up data on 20 of these 27 patients showed no recovery of BMD within 2-3 months after treatment. Longer term data at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment baseline, and 2 other did not show the increase in BMD above baseline expected in this adolescent population.

5.13 Ocular Abnormalities

Dry Eye

Dry eye has been reported in subjects during TRADENAME therapy. Patients who wear contact lenses may have trouble wearing them while on isotretinoin treatment and afterwards.

- **8 USE IN SPECIFIC POPULATIONS**

8.3 Nursing Mother

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from cip-isotretinoin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The effect on bone mineral density (BMD) of a single course of therapy with TRADENAME or a generic product of Accutane® (isotretinoin) was evaluated in a double-blind, randomized clinical trial involving 396 adolescents with severe recalcitrant nodular acne (mean age 15.4, range 12-17, 80% males). Following 20 weeks of treatment, there were no statistically significant differences between the

treatment groups. The mean changes in BMD from baseline for the overall study population were 1.8% for lumbar spine, -0.1% for total hip and - .3% for femoral neck. Mean BMD Z-scores declined from baseline at each of these sites (-0.053, -0.109 and -0.104 respectively). Out of 306 adolescent, 27 (8.8%) had clinically significant BMD decline, defined as $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral neck, including 2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck. Short-term follow-up DXA within 2-3 months after treatment showed no recovery of BMD. Longer-term follow up at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment baseline, and 2 others did not show the increase in BMD above baseline expected in this adolescent population. The significance of these changes in regard to long-term bone health and future fracture risk is unknown [see *Warnings and Precautions* (5.12)]. ...

There are spontaneous literature reports of premature epiphyseal closure in acne patients receiving recommended doses of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown. In a 20-week clinical trial that included 289 adolescents who had hand radiographs taken to assess bone age, a total of 9 patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded [see *Warnings and Precautions* (5.12)].

- **12 CLINICAL PHARMACOLOGY** – see Section 5 of this review

(b) (4)

Table 4: Efficacy Results at Week 20 (Study 1)

	<u>TRADENAME</u> <u>N=464</u>	<u>Isotretinoin*</u> <u>N=461</u>
<u>Nodular Lesions</u>		
<u>Mean Baseline</u>	<u>18.4</u>	<u>17.7</u>
<u>Count</u>	<u>-15.68</u>	<u>-15.62</u>
<u>Mean Reduction</u>		
<u>Success Rate^a</u>	<u>324 (70%)</u>	<u>344 (75%)</u>
<u>^a (Patients</u>		
<u>Achieving 90%</u>		
<u>Reduction</u>		

***generic product of Accutane[®]**

- **17 PATIENT COUNSELING INFORMATION**

Adolescent patients who participate in sports with repetitive impact should be informed that isotretinoin use may increase their risk of spondylolisthesis or hip growth plate injuries. [see Warnings and Precautions (5.12)]

- The applicant provided a **Medication Guide** as part of REMS (The iPLEDGE Program – Single Shared System for Isotretinoin). Based on the above data the Medication Guide for TRADENAME (isotretinoin) Capsule should be the same as for generic products of Accutane[®] (with exemption that TRADENAME (isotretinoin) Capsule could be taken without regard to meals). Medication Guide was review by Latonia M Ford [Patient Labeling Review; Division of Medical Policy Programs (DMPP); dated 04/30/12], Lynn M Panhozler and Sheetal Patel [Office of Prescription Drug Promotion (ODPD); Division of Prescription Drug Promotion (DPDP) and Division of Professional Drug Promotion/Division of Consumer Drug Promotion (DCDP) dated 05/08/12].

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 21951, TRADENAME (isotretinoin) Capsules, 10, 20, 30 and 40 mg pending agreement of the applicant with the recommended labeling revisions and “*Acceptable*” recommendation from the Office of Compliance regarding facilities inspections for the drug substance and drug product.

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of severe recalcitrant nodular acne

Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)

- Because of the risk of teratogenicity and to minimize fetal exposure, isotretinoin is available only through a restricted program under a REMS called iPLEDGE. Under the isotretinoin REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program.
- The REMS is necessary for TRADENAME (isotretinoin) Capsules to ensure the benefits of the drug outweigh the risks of teratogenic effects associated with fetal exposure to isotretinoin.
- The applicant provided the REMS, iPLEDGE, which is a single shared system for isotretinoin. The REMS consists of a Medication Guide, Elements to Assure Safe Use, Implementation System and Timetable for Submission of Assessments. In addition to the proposed REMS, the applicant submitted a “REMS supporting document”; all relevant proposed REMS materials including: enrollment forms, informed consents, educational and communication materials (appended to the proposed REMS)

Recommendation for other Postmarketing Requirements and Commitments

- PMC#1 Dissolution method development study

Conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

FDA will make a decision on the final dissolution method for your isotretinoin capsules after reviewing your dissolution method report. Once an agreement is reached on the final test method, use the final test method to propose final dissolution acceptance criteria for your isotretinoin capsules. Your proposal should be supported by dissolution data from at least the first three (3) validation lots of each capsule strength, and two (2) additional commercial batches of each strength. If the dissolution report provides for a new faster-release dissolution method (i.e., complete release/dissolution for all the strengths in < 90 minutes) and the provided data support the approval of this method, you may propose the implementation of a single-point dissolution criterion. Otherwise, implement at least a two-point criteria, with the first time point being a range of appropriate variability (ideally +/- 10%).

PMC Schedule Milestones:	Final Protocol Submission Date:	07/12
	Study Completion Date:	11/12
	Final Report Submission Date:	11/12

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

/s/

GORDANA DIGLISIC
05/08/2012