

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021951Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Class II Resubmission
	505(b)(2)
Application Number(s)	21-951
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Reviewer Name(s)	Denise Cook, M.D.
Review Completion Date	4/20/12
Established Name	Isotretinoin
(Proposed) Trade Name	Pending
Therapeutic Class	Oral Retinoid
Applicant	Cipher Pharmaceuticals Inc
Formulation(s)	Capsule – 10, 20, 30 & 40 mg
Dosing Regimen	0.5 mg/kg – 1.0 mg/kg/day in 2 divided doses
Indication(s)	Severe, recalcitrant nodular acne
Intended Population(s)	Ages 12 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that cip-isotretinoin 10 mg, 20 mg, 30 mg, and 40 mg capsule strengths, be approved for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

1.2 Risk Benefit Assessment

Cip-isotretinoin demonstrated in a double-blind, active-controlled trial with a currently marketed generic formulation of Accutane[®] (the listed drug) for this 505(b)(2) application, to be as efficacious as Accutane[®] in the treatment of severe recalcitrant nodular acne. The effect of food on the serum levels of cip-isotretinoin is much less than its effect on the serum levels of Accutane[®]. At the highest serum concentrations, with food, cip-isotretinoin and Accutane[®] are bioequivalent. In the fasted state, however, cip-isotretinoin levels are higher than Accutane[®] levels. This comparator clinical trial was undertaken to ascertain if this difference in bioavailability would translate into a significant difference in the incidence of the clinical safety issues associated with the use of Accutane[®]; namely psychiatric and CNS events, musculoskeletal events including changes in bone mineral density, hearing and vision impairment, and abnormal laboratory tests. The trial revealed that there was essentially no difference in the incidence of adverse reactions (events) between cip-isotretinoin and the reference product (a generic of Accutane[®]). Thus, approval of cip-isotretinoin for the treatment of severe recalcitrant nodular acne does not pose a different safety risk for the indicated population when compared to Accutane[®].

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The REMS for cip-isotretinoin will be the same as the REMS for all isotretinoin products namely, the iPLEDGE program.

1.4 Recommendations for Postmarket Requirements and Commitments

The following ONDQA postmarket commitment has been agreed upon:

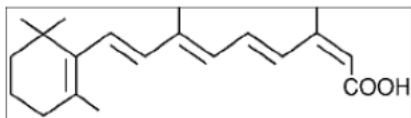
- Complete additional method development to reduce data variability, amount of surfactant and amount of enzyme used.
- Submit a PAS for the final method and acceptance criteria, with a request for FDA's review of the method under the IND before finalizing (see section 4.1 for more details).

2 Introduction and Regulatory Background

2.1 Product Information

Trade name (isotretinoin), a retinoid, will be available in 10 mg, 20 mg, 30 mg and 40 mg hard gelatin capsules for oral administration. Each capsule contains isotretinoin, stearyl macroglycerides, soybean oil, sorbitan monooleate and propyl gallate. Gelatin capsules contain the following dye systems: 10 mg – iron oxide (yellow) and titanium dioxide; 20 mg – (b) (4) titanium dioxide; 30 mg – (b) (4) titanium dioxide; and 40 mg – (b) (4) iron oxide (yellow, red, and black) and titanium dioxide.

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



Tables of Currently Available Treatments for Proposed Indications

Table 1: Retinoids (Oral)

Medications	Dose	List of Preparations
Oral Retinoid		
Oral isotretinoin	0.5mg/kg/day, increasing to 1mg/kg/day; total dose 120 to 150mg/kg over 20 weeks	Amnesteem, Claravis, Sotret

Table 2: Oral Antibiotics

Medications	Dose
Tetracycline	500mg twice daily
Doxycycline	50 to 100mg twice daily or 150mg once daily
Minocycline	50 to 100mg twice daily or 1mg/kg.day or the extended release formulation
Erythromycin	500mg twice daily
Trimethoprim-sulfamethoxazole	160mg/800mg once to twice daily
Azithromycin ^a	Intermittent dosing due to long drug half life; optimum regimen unknown

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

Note: Antibiotics are frequently used in clinical practice, but may not be approved for the indication.

^a Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95

Table 2a: Hormonal Agents

Medications	Dose
Combination oral contraceptives (estrogen/progestin)	Once daily
Spironolactone	25 to 200mg/day; doses of 50 to 100mg/day may be as effective as higher doses and reduce side effects

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient of cip-isotretinoin is the oral retinoid isotretinoin. Accutane was discontinued from marketing in the United States voluntarily by the innovator, Roche Pharmaceuticals in 2009. However, isotretinoin is still available in the US under the generic brand names Amnesteem, Sotret, Myorisan, and Claravis.

Accutane was first approved in 1982 to treat severe, recalcitrant nodular acne. Over the 30 years since approval, it is clear that isotretinoin is the only drug product that is efficacious in causing a cure in the treatment of nodular acne. A large majority of subjects only need one treatment course of 15-20 weeks.

Experience has confirmed, though, that isotretinoin is a human teratogen. Several programs have been instituted over the years in an attempt to prevent pregnancy in females of childbearing potential with varying degrees of success. The latest of these is a Risk and Evaluation Mitigation Strategy (REMS) called iPLEDGE. It is a restricted distribution program where all concerned parties including the pharmacy, physician, and

patient must be enrolled in iPLEDGE in order to dispense, prescribe, or take isotretinoin.

Isotretinoin has an adverse effect on many organ systems. These are mostly reversible but some have caused discontinuation of the drug product, permanent change, and some have resulted in death. These adverse reactions include but are not limited to, neuropsychiatric events such as suicide and aggressive and violent behavior; the bone system with losses in bone mineral density (BMD), particularly in adolescent patients who should have consistent increases in BMD; the musculoskeletal system with musculoskeletal pain, sometimes severe, with or without concomitant increases in serum CPK, delayed healing of bone fractures, and premature epiphyseal closure; endocrine and metabolism changes such as significant elevations of serum triglycerides with acute pancreatitis, elevations in serum cholesterol and LDL, decreases in HDL, elevations in liver function tests leading to frank hepatotoxicity, and elevations in serum glucose; the gastrointestinal system with new onset or worsening of inflammatory bowel disease; the hearing system with hearing impairment that may not be reversible; and the ophthalmic system with changes in visual acuity including night blindness.

2.4 Important Safety Issues With Consideration to Related Drugs

Acitretin, marketed as Soriatane[®], is an oral retinoid used in the treatment of severe psoriasis in adults. It is also a human teratogen but it has a different target population, mostly adults and mostly males. Most females are not prescribed this drug because of the long duration in which they would have to continue practicing birth control, for 3 years post treatment and because drinking alcohol while on acitretin converts the drug product into its parent compound, etretinate, which has a very long half-life, as it is stored in fat. Etretinate was not recommended for use in women of childbearing potential because of its prolonged half-life. Acitretin has much of the same adverse reaction profile as isotretinoin.

Summary of Presubmission Regulatory Activity Related to Submission

The following is the major presubmission regulatory activity since the filing of the original NDA on July 1, 2005.

- **“Approvable letter”** - 05/01/06:
 - 1. “The application did not establish, by way of bioavailability data comparing CIP-Isotretinoin to Accutane[®], an adequate basis for the Agency to rely on the previous finding of safety and effectiveness for the referenced listed drug, Accutane[®], to approve CIP-Isotretinoin. In addition, 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 and efficacy of

CIP-Isotretinoin. Your claim of no difference in terms of safety and effectiveness between CIP-Isotretinoin and the listed drug cannot be supported without clinical trial data.”

- To address deficiency #1, it was recommended that the sponsor either conduct a clinical safety and efficacy 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 or conduct a comparative population PK study in a suitable large number of subjects (>200 per arm) with severe recalcitrant nodular acne, either for 20 weeks duration.
 - 2. “ We acknowledge your commitment to inclusion in a risk management program, such as iPLEDGE, for prevention of fetal exposure to isotretinoin.
 - 3. “The NDA does not have an adequate demonstration of proportionality across the proposed dosage strengths. As isotretinoin is dosed on a mg/kg basis and as it is expected that multiple dosage units will be used to obtain doses in the 0.5-1mg/kg range, then the relationship between the different strength capsules will need to be determined for CIP-Isotretinoin.
 - 4. List the testing facilities that will perform quality control test on bulk drug substance, components, intermediates, container/closure system, and stability samples of finished drug product.
 - 5. Justify the in-process controls for the proposed commercial scale batches as the process parameters used in the manufacture of clinical batches differ from the proposed commercial scale process parameters.
 - 6. Establish multiple time points (30, 60, 120, and 240 minutes) based on typical dissolution profiles for the final (b) (4) dissolution test and for setting the acceptance criterion for each time point.
 - 7. The analytical method for the dissolution test is not the same as what had been used for the assay determination. If it is to be different, establish the LOQ, LOD for this specific method. In addition, establish the stability (shelf life) of the dissolution samples at room temperature stored in the HPLC vials.”
- **Complete Response to 05/01/06 action letter - 10/26/06 Resubmission:**
This application only addressed one deficiency outlined in the action letter, namely, dose proportionality across its different dosage forms. The application does not address the pivotal reason that marketability was denied, namely, the establishment of an adequate bridge to Accutane® such that the Agency could rely on the previous findings of safety and effectiveness for this RLD.
 - Contains 2 PK studies to address deficiency #3 (see above)
 - A reiteration of the sponsor’s previous rationale for the 505(b)(2) route
 - Has no clinical trial or comparative population PK study
 - Does not address any of the chemistry deficiencies
 - **Approvable letter” - 04/25/07:**
 - “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 is 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...

- 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 the doses of 1 mg/kg/day
- CMC deficiencies.”
- **Formal dispute resolution request** – 06/28/07; Meeting with Cipher 07/11/07 (Dr R. Tample, Dr. S. Walker, Dr.J Beitz,, and Ms. E. E. Dickinson); Letter – 08/10/07; Meeting with Cipher – 10/01/07 (stalled development discussion)
- **Response to Cipher request for formal dispute resolution** concerning the DDDP’s decision to issues an approvable letter for NDA 21-951 – 10/25/07:
 - “Clinical studies would be needed to adequately characterize the safety profile of CIP – Isotretinoin prior to approval”.
- **Guidance Meeting** – 01/28/07
- **Guidance Meeting** – 08/06/08
 - **SPA (protocol # ISOCT.08.01)** – 07/04/08
 - f/u Guidance meetings: 09/24/08; 09/29/08 (t-con); 01/07/09 (t-con)¹

After multiple discussions between the sponsor and the Agency concerning the Special Protocol Assessment for their phase 3 trial, agreements were reached on the following areas:

- The proposal for the neuropsychiatric assessment was acceptable
- The proposal for auditory assessment was acceptable
- The proposal for ophthalmologic assessment was acceptable
- Agreements were obtained on the co-primary and secondary efficacy endpoints
- The definitions for the ITT (intent-to-treat) and PP (per protocol) populations were acceptable and both populations would be considered together for establishing efficacy.²
- Agreements were reached considering musculoskeletal assessments except in the following area of bone mineral density (BMD) follow-up: the Agency recommended follow-up BMD on any adolescent who sustained $\geq 4\%$ BMD decline at lumbar spine or total hip or $\geq 5\%$ BMD decline at the femoral neck for up to 12 months.³

¹ Medical Officer Review: IND 64,927, pages 4-6, in DARRTS 4/14/2009.

² Special Protocol Agreement Letter, in DARRTS, dated 4/8/09.

³ Advice/Information Request Letter, in DARRTS, dated 2/01/10.

3 Ethics and Good Clinical Practices

Submission Quality and Integrity

The following data sources were provided by the sponsor and were review ready.
Electronic submission for Study ISOCT.08.01: <\\Cdsesub1\evsprod\NDA021951\0000>
Datasets for STUDY ISOCT.08.01:
<\\Cdsesub1\evsprod\NDA021951\0000\m5\datasets\isoct0801\analysis>

3.2 Compliance with Good Clinical Practices

This study was performed in accordance with standard operating procedures (SOPs) (b) (4) in effect at the time of the study. These SOPs were designed to ensure adherence to Good Clinical Practice (GCP) and ensure the protection of the patients, as required by the following directives in effect at the time the study was initiated:

- International Committee on Harmonization (ICH) E6: Good Clinical Practice Consolidated Guideline.
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996 Edinburgh, 2000, Washington, 2002)
- Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
- United States (US) 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Subject Consent and IRB approval.
- US Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.3 Financial Disclosures

The sponsor submitted a signed FDA Form 3454 in which it states that there were not any investigators that had anything to financially disclose.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Below is a summary of the recommendations by chemistry. The reader is referred to the reviews by Minerva Hughes, PhD in DARRTS 4/16/12 and by Tarun Mehta, PhD in DARRTS 4/18/12.

Dr. Hughes had two issues to evaluate in her review, that of the release designation for the cip-isotretinoin and the dissolution acceptance criteria for cip-isotretinoin.

Dr. Hughes concludes in her review that cip-isotretinoin will have an immediate release designation and the applicant has agreed with this designation.

The applicant and the Agency have come to an agreement concerning the dissolution acceptance criteria for the different strengths of cip-isotretinoin. On an interim basis the following table includes the acceptance criteria that are acceptable:

The following is the tentative agreement for a postmarket commitment (PMC) between chemistry and the applicant concerning the dissolution acceptance criteria that will be noted as a PMC in the action letter:

“1. Dissolution Method Development

- To complete the additional dissolution method optimization studies to, **(1)** evaluate the utility of a two-tiered dissolution method (similar to USP dissolution test 1) to address capsule rupture independently of dissolution, **(2)** identify different method parameters that allow for enzyme use in accordance with USP guidelines, and **(3)** identify a more suitable surfactant that can be used at lower concentrations, ideally <2%. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).
- To provide a dissolution method development report within 6 months of the date of the action letter under an amendment to the IND. A request for review of the dissolution report will be included in the cover page of their submission.

2. Dissolution Acceptance Limits (Final Criteria)

- To provide a proposal for the final acceptance criteria based on the dissolution profile data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength using the final dissolution method accepted by FDA. The acceptance criteria should be at least a two-point specification, with the first time point being a range of appropriate variability (ideally +/- 10%). The proposal for the final acceptance criteria will be submitted under a prior approval supplement (PAS) to the NDA within 14 months of the

date of the action letter and include the final dissolution method development report and all supportive data to support the proposed final dissolution specification.”⁴

In Dr. Mehta’s review, the 10 mg, 20 mg, and 30 mg capsule strengths will be given a 36-month shelf life and the 40 mg capsule strength will be give a 24 month shelf life. With the agreement above described in Dr. Hughes’ review, the specification for the drug product, according to Dr. Mehta is “now deemed satisfactory.”

Reviewer’s Comment: CMC has given an overall approval for cip-isotretinoin pending an acceptable “Overall Summary” from the Office of Compliance and adequate carton/container labels, in addition to the PMC agreement concerning the dissolution process.

4.2 Clinical Microbiology

Not applicable for this oral product.

4.3 Preclinical Pharmacology/Toxicology

From a clinical perspective, as the data in the relative bioavailability studies show that cip-isotretinoin is bioequivalent to Accutane under fed conditions, and fed conditions is the highest level attained, an adequate biobridge has been established such that cip-isotretinoin can rely on the Agency’s findings of safety, in part, for the listed drug Accutane®.

Dr. Jiaqin Yao’s review (in DARRTS 4/10/12) thus relied on the Agency’s findings of safety of Accutane® and the published literature. He has recommended approval of cip-isotretinoin from a pharmacology/toxicology perspective. There are no outstanding issues from a pharm/tox perspective.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

TRADENAME is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1 mg/kg/day, inhibits sebaceous gland function and keratinization. Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with isotretinoin and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. The exact mechanism of action of TRADENAME is unknown.

⁴ Biopharmaceutics Review: Office of New Drug Quality Assessment: Pages 1-4, in DARRTS 4/16/12.

4.4.2 Pharmacodynamics

The pharmacodynamics of TRADENAME is unknown.

4.4.3 Pharmacokinetics

All of the biopharmaceutics trials were conducted comparing cip-isotretinoin to Accutane[®], as the sponsor in this 505(b)(2) application is relying in part on prior efficacy and safety data obtained with the prior listed drug, Accutane[®]. The following is a summary of the clinical pharmacology findings from the clin/pharm reviews of Chinmay Shukla, PhD and previous reviews from the original application by Dennis Bashaw, PhD. The reader is referred to the complete reviews in DARRTS by Dr. Bashaw dated 4/21/2006, 4/9/2007 and by Dr. Shukla dated 4/12/12.

In the original NDA, the results of the relative bioavailability (BA) studies showed that under fed conditions, cip-isotretinoin was bioequivalent (BE) with Accutane[®] but that cip-isotretinoin was not bioequivalent with Accutane[®] under fasting conditions. Specifically, the exposure of cip-isotretinoin was approximately 2 fold higher than Accutane[®] when both the formulations were administered under fasting conditions.⁵ The results of dose proportionality studies done at that time demonstrated that the BA of cip-isotretinoin increased in a proportional manner between 10 mg and 30 mg strengths under both fasting and fed conditions. This thus indicates that the strengths that they had at that time, 10 mg, 20 mg, and 30 mg, could be used interchangeably to achieve the target dosing of 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses.

Also, in the previous submission, a food effect study was conducted with the 30 mg dose of cip-isotretinoin. The results indicated that there was a substantially larger food effect on Accutane[®] than on cip-isotretinoin, although there was still a significant food effect on cip-isotretinoin. In the presence of food, the systemic exposure (AUC) increased on average 1.5 times for the CIP-Isotretinoin formulation and approximately 2.5 times for the Accutane[®] formulation, while the peak exposure (C_{max}) to isotretinoin increased under fed conditions and was approximately 1.6 times and 2.7 times for the CIP-Isotretinoin and Accutane[®] formulations, respectively, compared to fasting conditions.⁶

In this submission, the sponsor is requesting to market an additional capsule strength of cip-isotretinoin, 40 mg. To support this, the sponsor submitted a food effect study and relative BA studies, one under fed conditions and one under fasted conditions comparing one 40 mg capsule to two 20 mg capsules of cip-isotretinoin. The result of

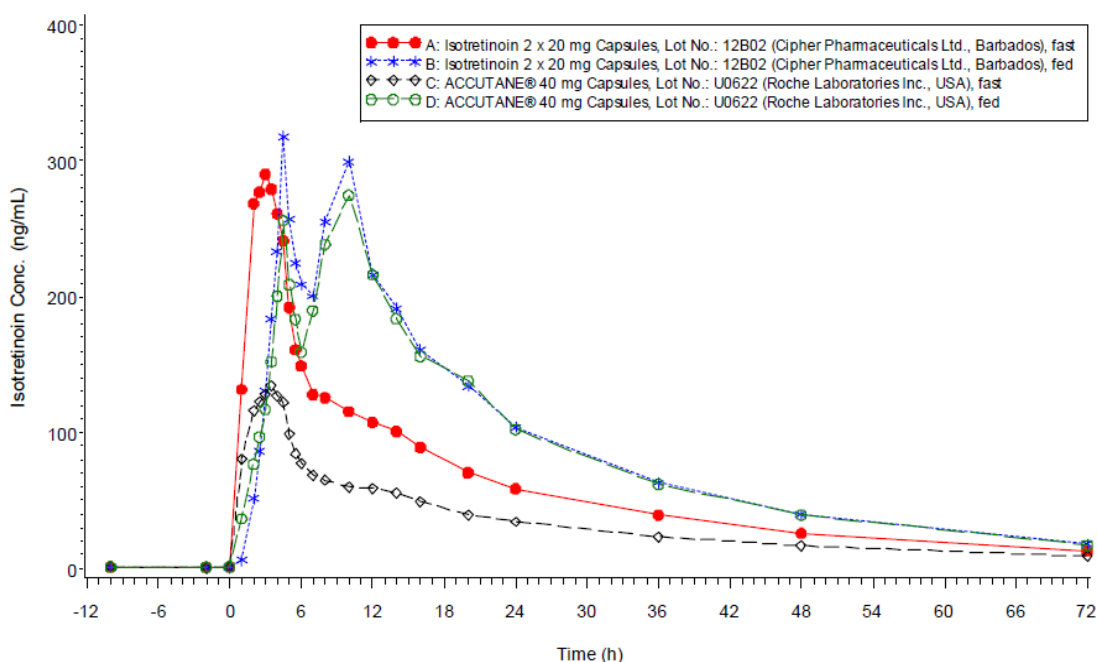
⁵ Shukla, Chinmay: Clinical Pharmacology Review, Section 1.3 – Findings from the Previous Submissions: page 2, in DARRTS 4/12/12.

⁶ Shukla, Chinmay: Clinical Pharmacology Review, Section 1.3 – Findings from the Previous Submissions: page 3, in DARRTS 4/12/12.

the food effect study was similar to the result of the food effect study of the 30 mg capsule. The results of the relative BA studies indicated that the 40 mg capsule and the two 20 mg capsules were BE under fed conditions but under fasting conditions the 40 mg capsule increased in a slightly less than dose proportional manner relative to two 20 mg capsules.

The systemic exposure of cip-isotretinoin under fasting conditions lie in between Accutane fasting and cip-isotretinoin and Accutane fed (see figure 1).

Figure 1⁷
Mean Concentration Versus Time Profile of Cip-isotretinoin and Accutane[®]
Administered Using Fasted or Fed Conditions (N = 57)



Thus, the slightly less than proportional increase in exposure with the 40 mg strength under fasting conditions is not expected to have an effect on efficacy because of the smaller magnitude of the food effect on cip-isotretinoin compared with Accutane and the fact that Accutane was originally approved in 1982 to be administered without regards to meals.⁸

⁷ Shukla, Chinmay: Clinical Pharmacology Review, Section 2.6.3.2, Figure 3, pg 19, in DARRTS .

⁸ Shukla, Chinmay: Clinical Pharmacology Review, Section 1.3 – Addition of a new strength: page 4, in DARRTS 4/12/12.

4.4.4. Pharmacometrics

The applicant completed a population pk study that was part of the phase 3 clinical trial between cip-isotretinoin and the reference product. This was reviewed by Dhananjay Marathe, PhD from the Division of Pharmacometrics. His conclusions and recommendations are summarized below. The reader is referred to his complete review in DARRTS, dated 4/12/12.

Dr. Marathe concluded the following:

- “• There was no difference in exposures between the two formulations under study usage where most doses were taken with the food but some taken after fasting.
- The efficacies were comparable and consistent with comparable isotretinoin exposures between pediatric and adult patients. Thus, no dose adjustment is recommended for pediatric patients.”⁹

Reviewer’s Comment: *Based on his review of the current biopharmaceutics trials, coupled with the reviews of the previously submitted biopharmaceutics trials under this NDA, Dr. Shukla has recommended an approval of all the dosage strengths of cip-isotretinoin (10 mg, 20 mg, 30 mg, and 40 mg). Based on the recommendations by both Drs. Shukla and Dr. Marathe, cip-isotretinoin can be dosed without regard to meals and no dosage adjustment needs to be made for the pediatric population. Clin/pharm does not have any outstanding issues or post-marketing requirements.*

⁹ Dhananjay Marathe, PhD: Clinical Pharmacology Review: Appendix Pharmacometrics Review: Section 1.2 Recommendations, page 62, in DARRTS 4/12/12.

5 Sources of Clinical Data

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5.1 Tables of Studies/Clinical Trials

Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
BA	ISOPK.02.04 (02-444)	5.3.1.1.1	To compare the bioavailability of CIP-ISOTRETINOIN capsules (30 mg) in healthy, non-smoking, male subjects, under fasting and fed conditions.	Open-label, single-dose, randomized, two-treatment, two sequence, two period, crossover bioavailability study.	Test: Treatment A: CIP-ISOTRETINOIN 30 mg Capsules; fasting; oral; Lot # 27C02 Treatment B: CIP-ISOTRETINOIN 30 mg Capsules; fed; oral; Lot # 27C02	18 (18/0), healthy volunteers, 28 (18-45)
BA	ISOPK.02.03 (02-443)	5.3.1.1.2	To assess the dose proportionality between different strengths of CIP-ISOTRETINOIN capsules (5 mg, 15 mg and 30 mg) in healthy, male subjects, under fed conditions.	Open-label, single-dose, randomized, three-treatment, six sequence, three-period, crossover study.	Test: Treatment A: CIP-ISOTRETINOIN 5 mg Capsules; oral; Lot 4C02 Treatment B: CIP-ISOTRETINOIN 15 mg Capsules; fed; oral; Lot 8B02 Treatment C: CIP-ISOTRETINOIN 30 mg Capsules; oral Lot 27C02	30 (30/0), healthy volunteers, 34 (24-52)

Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
BA	ISOPK.06.01 (2006-1232)	5.3.1.1.3	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN Capsules 3 x 10 mg and CIP-ISOTRETINOIN 1 x 30 mg after a single dose in healthy male and female subjects under fasting conditions	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	A: CIP-ISOTRETINOIN 3 x 10 mg Capsules fasting; oral; Lot # 5D04 B: CIP-ISOTRETINOIN 30 mg Capsules; fasting; oral; Lot # 29G04	54 (33/21), healthy volunteers, 37 (21-54)
BA	ISOPK.06.02 (2006-1233)	5.3.1.1.4	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN Capsules 3 x 10 mg and CIP-ISOTRETINOIN 1 x 30 mg after a single dose in healthy male and female subjects under fed conditions	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	A: CIP-ISOTRETINOIN 3 x 10 mg Capsules fed; oral; Lot # 5D04 B: CIP-ISOTRETINOIN 30 mg Capsules fed; oral; Lot # 29G04	54 (30/24), healthy volunteers, 35 (21-55)
BA	ISOPK.08.02 (82234)	5.3.1.1.5	To compare the bioavailability of CIP-ISOTRETINOIN Capsules (40 mg) in healthy, non-smoking, male subjects, under fasting and fed conditions.	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	A: CIP-ISOTRETINOIN 40 mg Capsules; fed; oral; Lot # IJ08 B: CIP-ISOTRETINOIN 40 mg Capsules; fasting; oral; Lot # IJ08	14 (14M), healthy volunteers, 37 (21-52)

Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
BA	ISOPK.09.01 (100005)	5.3.1.1.6	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN Capsules 2 x 20 mg and CIP-ISOTRETINOIN 1 x 40 mg after a single dose in healthy male and female subjects under fed conditions	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	A: CIP-ISOTRETINOIN 2 x 20 mg Capsules; oral; Lot # 5D102 B: CIP-ISOTRETINOIN 1 x 40 mg Capsules; oral; Lot # 5D103	49 (49M), healthy volunteers, 38 (20-55)
BA	ISOPK.09.02 (100004)	5.3.1.1.7	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN Capsules 2 x 20 mg and CIP-ISOTRETINOIN 1 x 40 mg after a single dose in healthy male and female subjects under fasting conditions	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	A: CIP-ISOTRETINOIN 2 x 20 mg Capsules; oral; Lot # 5D102 B: CIP-ISOTRETINOIN 1 x 40 mg Capsules; oral; Lot # 5D103	50 (50M), healthy volunteers, 38 (22-52)
Comparative BA	ISOPK.03.04 (2003-627)	5.3.1.2.1	To evaluate the comparative bioavailability of CIP-ISOTRETINOIN vs. Accutane®.	Open-label, single-dose, randomized, four-period, twelve sequence, four-treatment, crossover comparative bioavailability study.	Test: CIP-ISOTRETINOIN 40 mg (20 x 2) Capsules; oral; Lot # 28A02 Reference: Accutane® 40 mg Capsule; oral; Lot # U0622	60 (40/20), healthy volunteers, 36 y (21-55)

Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
Comparative BA	ISOPK.04.02 (2004-727)	5.3.1.2.2	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN capsules 20 mg and Accutane® capsules 20 mg (Roche Laboratories Inc., USA), after a single-dose in healthy subjects under fed conditions.	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study.	Test: CIP-ISOTRETINOIN 20 mg Capsules; oral; Lot # 28A02 Reference: Accutane® 20 mg Capsules; oral Lot # U3629	54 (51/3) healthy volunteers, 36 (18-56)
Comparative BA	ISOPK.04.03 (2004-734)	5.3.1.2.3	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN capsules 10 mg and Accutane® capsules 10 mg, after a single-dose in healthy subjects under fed conditions.	Open-label, single-dose, randomized, three-period, six-sequence, three treatment, crossover comparative bioavailability study.	Test: CIP-ISOTRETINOIN Caps 10 mg; ; oral; Lot # 16F032 Reference: Accutane® Capsules 10 mg; oral; Lot # U2624	54 (40/14) healthy volunteers, 38 (21-54)
Comparative BA	ISOPK.03.02 (2003-666)	5.3.1.2.4	To evaluate the comparative bioavailability between CIP-ISOTRETINOIN capsules 2 x 20 mg and Accutane® capsules 40 mg after multiple 40 mg doses in healthy male and female subjects under fed conditions at steady-state.	Open-label, multiple-dose, randomized, two-period, two-sequence, two treatment, crossover study.	Test: Treatment A CIP-ISOTRETINOIN Capsules 20 mg; [2 x 20 mg administered twice a day (q12h); fed; 11 days]; oral; Lot # 28A02, (Reference): Treatment B Accutane® Capsules 40 mg; [1 x 40 mg administered twice a day (q12h); fed; 11 days] Lot # U0625 50	47 (45/2), healthy volunteers, 36 (19-49)
Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
Comparative BA	ISOPK.02.01 (02-441)	5.2.1.2.5	To define pharmacokinetics and to determine relative bioavailability of CIP-ISOTRETINOIN 30 mg Capsules versus Accutane® 40 mg Capsules, in healthy, male and female subjects, under fed and fasting conditions.	Open-label, single-dose, randomized, three-treatment, six sequence, three period, crossover bioavailability study.	Test: Treatment A: CIP-ISOTRETINOIN 30 mg Capsules; fed; oral; Lot # 27C02 Reference: Treatment B: Accutane® 40 mg Capsules; fed; oral; Lot # U0605 Treatment C: Accutane® 40 mg Capsules; fasting; oral; Lot # U0605	36 (21/15), healthy volunteers, 35 (18-50)
Comparative BA	ISOPK.02.02 (02-442)	5.2.1.2.6	To assess the pharmacokinetic parameters and to determine relative bioavailability of a new formulation of CIP-ISOTRETINOIN 30 mg Capsules versus Accutane® 40 mg Capsules, given once a day, in healthy, male and female subjects, under fed conditions.	Open-label, multiple-dose, randomized, two-treatment, two sequence, two-period, crossover relative bioavailability study.	(Test): Treatment A: A single dose of CIP-ISOTRETINOIN 30 mg Capsules; fed; for 11 days; oral; Lot # 27C02; (Reference): Treatment B: A single dose of Accutane® 40 mg Capsules; fed; oral; for 11 days; Lot # U0605;	36 (17/11), healthy volunteers, 35 (20-54)

Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
Population PK (sub-study of Phase III study)	C10-2306	5.3.3.5.1	To determine if there is a difference in steady-state exposure between the CIP-ISOTRETINOIN formulation and a reference comparator formulation under study usage.	Double-blind, active control, parallel group, multi-center study, consisting of a 20-week treatment phase and a 4-week follow-up phase.	Test: CIP-ISOTRETINOIN at a dose of approximately 0.5 mg/kg/day for the first 4 weeks and approximately 1 mg/kg/day for Weeks 5 through 20. The total daily dose was to be divided in two and taken with meals, at breakfast and dinner. In addition, patients were instructed to take their last dose prior to Visits 4, 6 and 7 with a meal; however, their last dose prior to Visits 3, 5 and 8 was to be taken under fasting conditions. Reference: A marketed generic formulation at a dose of approximately 0.5 mg/kg/day for the first 4 weeks and approximately 1 mg/kg/day for Weeks 5 through 20. The total daily dose was to be divided in two and taken with meals, at breakfast and dinner. In addition, patients were instructed to take their last dose prior to Visits 4, 6 and 7 with a meal; however, their last dose prior to Visits 3, 5 and 8 was to be taken under fasting conditions.	522
Type of Study	Study Ref. No.	Full Study Report Location	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product Lot No.]	Subjects (No. (M/F), type, Age: mean (range))
Phase III	ISOCT.08.01	5.3.5.1.1	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 to evaluate the safety profile of CIP-ISOTRETINOIN.	Double-blind, randomized, Phase III, active control, parallel-group, multicenter study.	Test: 10 and 20 mg capsules at an initial titration dose of approximately 0.5 mg/kg/day divided into 2 doses with meals for the first 4 weeks, followed by approximately 1 mg/kg/day divided into 2 doses with meals for 16 weeks. Reference: 10 mg and 20 mg capsules at an initial titration dose of approximately 0.5 mg/kg/day divided into 2 doses with meals for the first 4 weeks, followed by approximately 1 mg/kg/day divided into 2 doses with meals for 16 weeks.	795 (560/3650), acne patients, 20.8 (12 – 52)

Source: NDA 21-951: Module 5.2, Tabular Listing of all Clinical Studies, Pages 1-7.

5.2 Review Strategy

There are 13 biopharmaceutics trials associated with this NDA. All but three of them were reviewed in previous submissions. Three new trials concerning a 40 mg capsule strength, ISOPK.08.01, ISOPK.09.01, and ISOPK.09.02 were reviewed in this cycle by Chinmay Shukla, PhD (see section 4.4). Dhananjay Marathe, PhD evaluated the population pk trial which was part of the comparative clinical trial, ISOCT.08.01.

The application consists of one comparative clinical trial, ISOCT.08.01, between cip-isotretinoin and a marketed generic of Accutane[®]. The trial is reviewed in detail to establish efficacy of cip-isotretinoin, verified by Yuqing Tang, PhD in the Division of Biostatistics, and safety as it compares to this reference drug product. Multiple safety concerns that are known with isotretinoin are addressed in this clinical trial and the following divisions provided consultative input for their area of expertise:

- DRUP – Bone mineral density and musculoskeletal evaluation
- DPP – Psychiatry evaluation
- CDRH – Audiology evaluation
- DTOP – Ophthalmology evaluation

In addition consults were submitted to the following:

- DMPP – Review patient labeling to ensure it is accurate and easily understood
- OPDP – Review PI/patient labeling from a promotional and advertising perspective
- OSE (DMEPA) – Review carton/container labeling
- OSE (DRISK) – Review language for ETASU products
- Maternal Health – Review the Pregnancy and Nursing Mothers sections/subsections of the labeling

As this is a 505(b)(2) application, the biopharmaceutics trials form an important basis for the establishment of a biobridge of cip-isotretinoin to the listed product, Accutane[®] or its currently marketed generics. This, in conjunction with the comparative safety and efficacy data from the clinical trial, will form the basis for cip-isotretinoin to borrow the findings of safety for Accutane[®] to apply to its drug product.

5.3 Discussion of Individual Studies/Clinical Trials

This was a double-blind, randomized, Phase 3, active-control, parallel-group, multicenter trial 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 product¹⁰, in a 1:1 ratio stratified by gender and study site. Trial medication was taken at

¹⁰Because Accutane became unavailable before study start, a marketed generic isotretinoin product (Amnesteem, Mylan Inc) was selected as the reference product for the study. During the course of study execution, Amnesteem was put on back order after Accutane was withdrawn from the market. To maintain supply of product, a second marketed generic isotretinoin product (Claravis, Barr Pharmaceuticals Inc.), was used as a Reference Product on a temporary basis.

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 (breakfast and dinner) for 16 weeks.¹¹ 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 (see table 3).

Table 3
Trial Design

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Screening Day -45 to 0	Baseline	0.5 mg/kg/day			1 mg/kg/day				Follow-up
		Week 2	Week 4		Week 8	Week 12	Week 16	Week 20 ^b	Week 24
Visit 1	Visit ^a 2	Visit 3	Visit 4		Visit 5	Visit 6	Visit 7	Visit 8	Visit 9

a: First drug dosing on following day.

b: The Week 20 (Visit 8) was considered to be the end of treatment (EOT) visit.

Source: NDA 21-951: Clinical Study Report: ISOCT: 08:01: table 9, page 45

Assessing the safety of cip-isotretinoin as it compares to already marketed isotretinoin, because of its higher bioavailability in the fasted state, was a main component of this comparative non-inferiority trial. The protocol had in place assessments to detect psychiatric adverse events (C-SSRS, GAD-7, PHQ-8 assessment, psychosis assessment), eye disorders, bone mineral density and bone age changes (DEXA, X-ray hand, and Tanner staging), ear disorders (audiology testing in a subset of subjects at 25% of study sites), and laboratory abnormalities. All pediatric patients were required to have DEXA scans, X-ray of the hand, and Tanner assessments. Adults were requested to have DEXA scans but not mandated. Laboratory assessments included the following:

- Hematology parameters: red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, differential count, platelet count, and Hb-A1c (only in patients who presented with diabetes mellitus, Types I and II at Screening)
- Serum chemistry parameters included: glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma-glutamyltransferase (GGT), total bilirubin, sodium, potassium, chloride, bicarbonate (HCO₃), calcium, phosphate, creatine kinase (CK), and 25-hydroxyvitamin D (at Screening only in pediatric patients 12-17 years old and the subset of adult patients enrolled in the bone study).
- Lipid profile parameters: total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and triglycerides (subjects were instructed to fast prior to these).

¹¹ The titration was probably done because some centers were in Canada and their PI requires to start with 0.5 mg/kg/day in 2 divided doses for 4 weeks.

- Urinalysis parameters included: pH, specific gravity, glucose, ketones, bilirubin, protein, and occult blood.

Safety data was also obtained through physical examinations, vital signs, and musculoskeletal assessments. Table 4 describes the schedule of assessments for the study participants.

Table 4
Schedule of Assessments

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Visit #	1	2	3	4	5	6	7	8	9
	Screening (within 45 ^a days of baseline)	Baseline (first drug dosing on following day)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 follow- up visit
			0.5 mg/kg/day ^b dose period		1 mg/kg/day ^b dose period				
Informed consent	×								
Demographics, medical history	×								
Inclusion/exclusion criteria	×	×							
Physical examination	×							×	
Vital signs, weight	×	×		×	×	×	×	×	×
Concomitant medication	×	×	×	×	×	×	×	×	×
Review Previous Labs		×	×	×	×	×	×	×	×
Laboratory tests: Hematology Serum chemistry Urinalysis	×			×	×	×	×	×	×
Liver function tests	×		×	×	×	×	×	×	×
Lipid profile	×		×		×			×	
Pregnancy test (for females of childbearing potential)	×	×		×	×	×	×	×	×
Pharmacokinetics blood draw	×		×	×	×	×	×	×	
Urinalysis	×			×	×	×	×	×	×
<i>DEXA (all pediatric patients and sub-set of adult patients)</i>	×							×	
<i>X-ray hand (pediatric patients only)</i>	×							×	
<i>Tanner staging (pediatric patients only)</i>		×						×	
Ophthalmic testing/ Visual screening	×			×	×	×	×	×	×

Source: NDA 21-951: Clinical Study Report, Table 9-4, page 61

Table 4
Schedule of Study Assessments (con't)

Visit #	1	2	3	4	5	6	7	8	9
	Screening (within 45 ^a days of baseline)	Baseline (first drug dosing on following day)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 follow- up visit
			0.5 mg/kg/day ^b dose period		1 mg/kg/day ^b dose period				
<i>Audiology testing (at selected sites)</i>	×							×	
Contraceptive counseling	×	×		×	×	×	×	×	
Randomization		×							
Lesion count (nodules only)	×								
Lesion count (nodules and inflammatory lesions)		×		×	×	×	×	×	
Physician global assessment		×						×	
Patient assessment of efficacy								×	
Adverse events			×	×	×	×	×	×	×
Drug dispensing		×		×	×	×	×		
Unused study drug collection				×	×	×	×	×	
SCID-CT	×								
C-SSRS	×	×	×	×	×	×	×	×	×
GAD-7		×		×	×	×	×	×	×
PHQ-8 assessment	×	×	×	×	×	×	×	×	×
Psychosis assessment		×		×	×	×	×	×	×
Musculoskeletal questions		×		×	×	×	×	×	×

a: Except for women who needed to begin 2 forms of birth control and/or who needed a second urine pregnancy test during the first 5 days of their menstrual cycle and patients screened for enrollment in the bone study who needed to be supplemented for low 25-hydroxyvitamin D levels.

b: The specified dosage was divided into two daily doses.

SCID-CT- Psychiatric tool used at screening to exclude subjects with a lifetime history of psychosis or a major depressive or manic episode in the previous year.

Source: NDA 21-951: Clinical Study Report, Table 9-4, page 61.

A Data Safety Monitoring Board (DSMB) was chartered and reviewed the trial-related safety data four (4) times during the course of the trial. The Board consisted of a statistician, a psychiatrist, and a board certified dermatologist. After each of the DSMB meetings, the trial was allowed to continue without any modifications.

Efficacy assessments included lesion counts and the Physician's Global Severity Assessment (PGSA). Lesion counts were performed at Screening, Baseline, and Visit 4 through Visit 8. Qualified medical practitioners or authorized designees who were blinded to treatment group assignment made counts of nodules and inflammatory lesions (papules and pustules) in the facial and truncal area. Where possible, the same individual performed all evaluations for a patient. The PGSA was performed at visit 2 and visit 8 (week 20). This variable was a secondary efficacy variable and only applied to facial lesions. Table 5 describes the PGSA scale.

Table 5
Physician's Global Severity Assessment (PGSA)

Description	Grade	Acne Disease Status
Clear	0	No nodules, pustules or papules visible.
Almost clear	1	Hardly visible. A few scattered comedones, few small papules, and very few pustules.
Mild	2	Easily recognizable, less than ½ face involved. Many comedones, papules, and pustules.
Moderate	3	More than ½ face involved. Numerous comedones, papules, and pustules.
Severe	4	Entire face involved. Covered with comedones, numerous papules and pustules and many nodules and cysts.
Very severe	5	Highly inflammatory acne covering the affected area, with many nodules and cysts present.

Source: NDA 21-951: Study Report, table 9-5, page 63.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication by the applicant is as follows: “(b) (4) is indicated for the treatment of severe recalcitrant nodular acne.”

Reviewer's Comment: *This is the applicant's proposed indication. It will be modified to the following indication, “TRADENAME is indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.” This is to reflect the*

population evaluated in the clinical trial and to comply with PLR labeling requirements.

(b) (4) the applicant's second proposed name has been rejected, as was the first name proposed, (b) (4).

6.1.1 Methods

The comparator trial of cip-isotretinoin to a currently marketed generic of Accutane[®], trial ISOCT.08.01, was reviewed, along with the clinical overview to support the efficacy of cip-isotretinoin in the treatment of severe recalcitrant nodular acne.

6.1.2 Demographics

A total of 925 subjects were randomized in the trial, 464 on cip-isotretinoin (CIP) and 461 on reference product (RP). Enrolled patients were between the ages of 12 and 52, with 43% of the enrolled subjects < 18 years old. Approximately 60% of subjects in both arms were male, predominately white (87%) and non-Hispanic (87%). The overwhelming majority of the subjects were from the United States (81%). Table 6 outlines the demographics for the population in trial ISOCT.08.01.

Table 6
Baseline Demographics
ITT Population

	CIP- ISOTRETINOIN (N = 464)	Reference Product (N = 461)	Overall (N = 925)
Age (yrs)			
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
Age Group - n (%) - years			
12-14	62 (13.4)	41 (8.9)	103 (11.1)
15-17	143 (30.8)	151 (32.8)	294 (31.8)
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)
Gender - n (%)			
Male	277 (59.7)	283 (61.4)	560 (60.5)
Female	187 (40.3)	178 (38.6)	365 (39.5)
Geographic Region - n (%)			
US	380 (81.9)	373 (80.9)	753 (81.4)
Canada	84 (18.1)	88 (19.1)	172 (18.6)
Ethnicity - n (%)			
Hispanic	59 (12.7)	63 (13.7)	122 (13.2)
Non-Hispanic	405 (87.3)	398 (86.3)	803 (86.8)
Race - n (%)			
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)

Source: NDA 21-951: Clinical Study Report, table 11-2, page 95. Statistical Review agrees: table 4, page 9: DARRTS 4/4/12.

Table 7 describes the baseline disease characteristics for the ITT population. Everyone in the trial had at least 10 nodules at baseline, as required by the inclusion criteria. 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 PGSA baseline score of 4 (severe). As the PGSA only evaluated facial nodular acne, those subjects with less than severe PSGA scores in the face, also had truncal nodular acne.

Table 7
Baseline Disease Characteristics
ITT Population

	CIP- ISOTRETINOIN (N = 464)	Reference Product (N = 461)	Overall (N = 925)
Baseline Nodular Lesion Count			
N	464	461	925
Mean (SD)	18.4 (14.7)	17.7 (10.8)	18.0 (12.9)
Median	14.0	14.0	14.0
Range	10, 126	10, 100	10, 126
P value ^a	0.2830		
Number of patients with:			
≤ 14 Lesions at Baseline	263 (56.7)	256 (55.5)	519 (56.1)
> 14 Lesions at Baseline	201 (43.3)	205 (44.5)	406 (43.9)
Baseline Inflammatory Lesion Count			
N	464	461	925
Mean (SD)	37.8 (31.3)	38.4 (34.5)	38.1 (33.0)
Median	29.0	29.0	29.0
Range	0, 175	0, 245	0, 245
P value ^a	0.9465		

Baseline PGSA Score^b

Not Assessed	8 (1.7)	4 (0.9)	12 (1.3)
1 = Almost Clear	3 (0.6)	2 (0.4)	5 (0.5)
2 = Mild	11 (2.4)	10 (2.2)	21 (2.3)
3 = Moderate	49 (10.6)	60 (13.0)	109 (11.8)
4 = Severe	329 (70.9)	322 (69.8)	651 (70.4)
5 = Very Severe	64 (13.8)	63 (13.7)	127 (13.7)

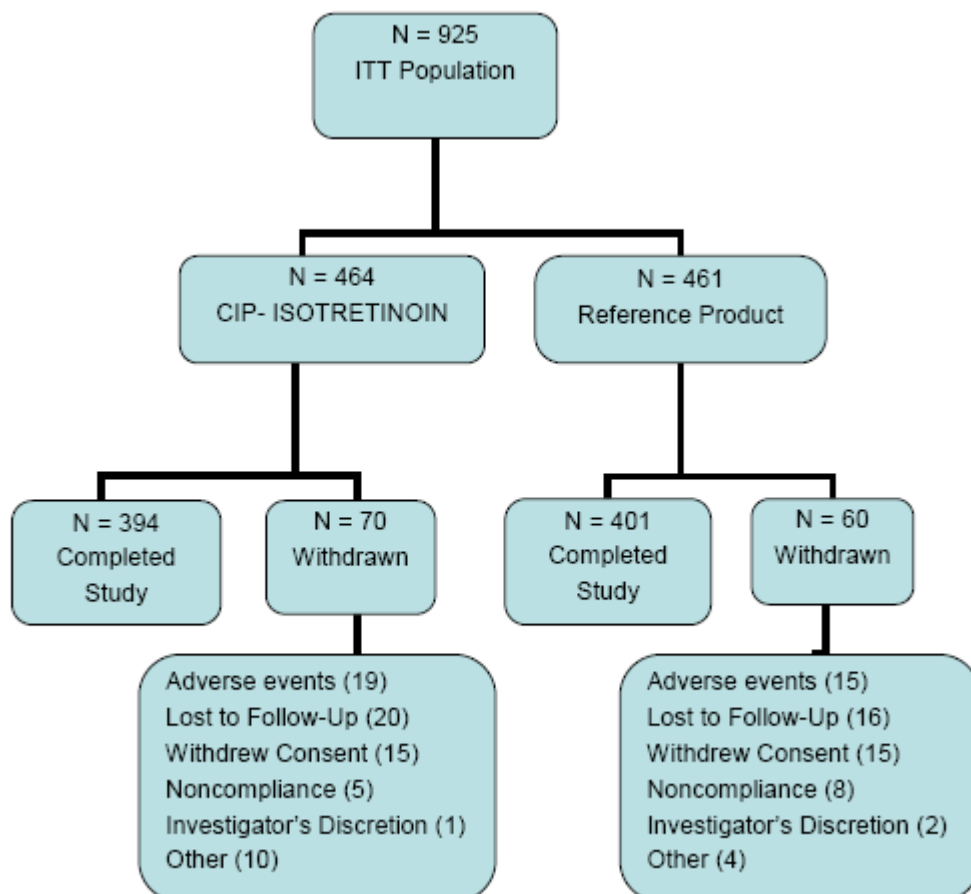
Source: NDA 21-951: Clinical Study Report: Table 11-3, page 99. Statistical Review agrees, table 5, page 10: DARRTS 4/4/12.

6.1.3 Subject Disposition

Of the 925 subjects who were randomized, a total of 813 (87.9%) subjects completed the treatment phase of the study and 795 (85.9%) patients completed the follow-up phase.

Overall 130 (14.1%) subjects 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 subject was lost to follow-up: 20 (4.3%) subject in the cip-isotretinoin group and 16 (3.5%) subjects in the reference product group. In addition, 34 (3.7%) subjects 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%) subjects, 15 in each group (3.2% in the CIP group and 3.3% in the RP group), withdrew their consent. Figure 2 depicts the subject disposition.

Figure 2
Disposition of Subjects
ITT Population¹²



Reviewer's Comment: On review of the data listings, most of the subjects who withdrew due to "other" were because of relocation or conflicts with work or school schedule. Other reasons included death of a parent and incarceration.

Of the 925 subjects included in the ITT population, 724 (78.2%) were also included in the 'per protocol' (PP) population: 363 (78.2%) in the cip-isotretinoin group and 361 (78.3%) in the reference product group. A total of 201 (21.7%) of the subjects were excluded from the PP population: 101 (21.8%) in the CIP group and 100 (21.7%) in the RP group. In both groups, the most common reason for exclusion was noncompliance with study treatment regimen: 76 (16.4%) subjects in the cip-isotretinoin group and 75

¹² NDA 21-951: Clinical Study Report, Figure 10-1, page 90.

(16.3%) subjects in the reference product group. Table 8 describes the details of the PP population.

Table 8
Subjects Excluded from the PP Population

	CIP- ISOTRETINOIN N = 464	Reference Product N = 461	Overall N = 925
Patients Excluded from PP Population	101 (21.8)	100 (21.7)	201 (21.7)
Reason for Exclusion ^a n (%)			
Actual use of study product not according to randomization	2 (0.4)	2 (0.4)	4 (0.4)
Received medication from wrong treatment group	1 (0.2)	1 (0.2)	2 (0.4)
Received another patient's medication	1 (0.2)	1 (0.2)	2 (0.4)
No Week 20 nodular lesions count	61 (13.1)	51 (11.1)	112 (12.1)
Noncompliance with study schedule/procedures.	0	2 (0.4)	2 (0.2)
Noncompliance with study treatment regimen	76 (16.4)	75 (16.3)	151 (16.3)
Use of prohibited concomitant medications	1 (0.2)	3 (0.7)	4 (0.4)

Source: NDA 21-951: Clinical Study Report, table 10-2, page 91.

Reviewer's Comment: The reasons for exclusion from the per protocol population for cip-isotretinoin and a currently marketed generic of Accutane[®] (the reference product) are basically the same. Notably, noncompliance with the study treatment regimen was the same for both groups.

6.1.4 Analysis of Primary Endpoint(s)

This trial was a non-inferiority trial comparing Cip-isotretinoin to a currently marketed generic of Accutane[®]. Cip-isotretinoin was considered non-inferior to the reference product if: (1) the upper bound of the 2-sided 95% CI for the treatment difference (cip-isotretinoin minus RP) was ≤ 4 for the total nodular lesion count; and (2) if the lower bound of the 95% CI for the treatment difference (cip-isotretinoin minus RP) was greater than or equal to (b) (4) for the proportion of patients who achieve at least a 90% reduction in total number of nodular lesions.

Reviewer's Comment: For a non-inferiority trial, both the intent-to-treat (ITT) and per protocol (PP) analyses are considered together for establishing efficacy.

The results for both co-primary endpoints along with the baseline disease severity are presented in table 9.

Table 9
Analysis Results for the Co-Primary Endpoints
ITT and PP Populations

	CIP-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 DARTS 4/4/12.

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

Reviewer's Comment: The non-inferiority margin of 10% is a recommended margin by the Agency but is not required. When looking at the results of both the ITT and PP populations, in this reviewer's opinion, cip-isotretinoin is as efficacious in the treatment of nodular acne as is the reference product, isotretinoin. For all subjects who completed the trial, cip-isotretinoin met the non-inferiority margin (b) (4). Clinically, by missing the non-inferiority margin of 10% by only (b) (4), this will not be clinically significant when treating patients with the drug product.

6.1.5 Analysis of Secondary Endpoints(s)

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 (b) (4).

The applicant did not specify the PGSA score as one of the inclusion criteria. There are 3 subjects in CIP arm and 2 subjects in RP arm that were enrolled with a PGSA score of "Almost Clear". Therefore, it is difficult to interpret the results of proportion of subjects achieving "Clear" or "Almost Clear" at Week 20. Descriptively, there are 326 out of 464 (70%) subjects for the cip-isotretinoin arm and 351 out of 461 (76%) subjects for the reference product that have a PGSA score of "Clear" (0) or "Almost Clear" (1) at Week 20 based on the ITT population.

Reviewer's Comment: *Despite the discrepancies, the secondary endpoint supports the co-primary endpoints.*

6.1.6 Other Endpoints

No other endpoints were explored in this trial.

6.1.7 Subpopulations

The following is the subgroup analysis from the biostatistics review by Dr. Yuqing Tang.

The two co-primary endpoints were investigated by gender, age group (12-17 or ≥ 18), and total baseline nodular lesion count (< 14 or ≥ 14). As White subjects account for more than 86% and all other categories account for less than 6% of the total subjects enrolled, it did not allow for a meaningful analysis of subgroups defined by race. The results are presented in tables 10 and 11.

Overall, the decrease in total nodular lesion count is similar in the CIP arm and RP arms. However the proportion of subjects with at least 90% clearance was greater with the RP in all subpopulations. Female subjects reported a notably larger success rate (75.9%) of 90% clearance compared to that (65.7%) of male subjects in CIP arm. Subjects who had more nodular lesions (≥ 14) in both arms had a significantly larger decrease in the total lesion counts than those that had less nodular lesions (< 14).

Table 10
Mean Change in Total Lesion Counts by Gender,
Age, and Baseline Severity – ITT Population

		CIP-Isotretinoin N=464	Reference Product N=461
Gender	Male	-17.0 (16.5)	-16.5 (11.6)
	Female	-13.8 (9.0)	-14.3 (8.6)
Age	<18 yrs	-17.4 (16.8)	-17.5 (12.6)
	>=18 yrs	-14.3 (11.2)	-14.3 (8.6)
Baseline Lesion Counts	<14	-9.5 (3.3)	-10.1 (2.8)
	>=14	-21.4 (17.4)	-21.0 (12.5)

Source: NDA 21-951: Statistical Review: table 9, page 14 in DAARTS 4/4/12.

Table 11
Success rate of 90% Clearance by Gender,
Age, and Baseline Severity – ITT Population

		CIP-Isotretinoin N=464	Reference Product N=461
Gender	Male	182/277 (65.7%)	208/283 (73.5%)
	Female	142/187 (75.9%)	136/178 (76.4%)
Age	<18 yrs	141/205 (68.8%)	145/192 (75.5%)
	>=18 yrs	183/259 (70.7%)	199/269 (74.0%)
Baseline Lesion Counts	<14	159/224 (71.0%)	175/227 (77.1%)
	>=14	165/240 (68.8%)	169/234 (72.2%)

Source: NDA 21-951: Statistical Review: table 10, page 15 in DAARTS 4/4/12.

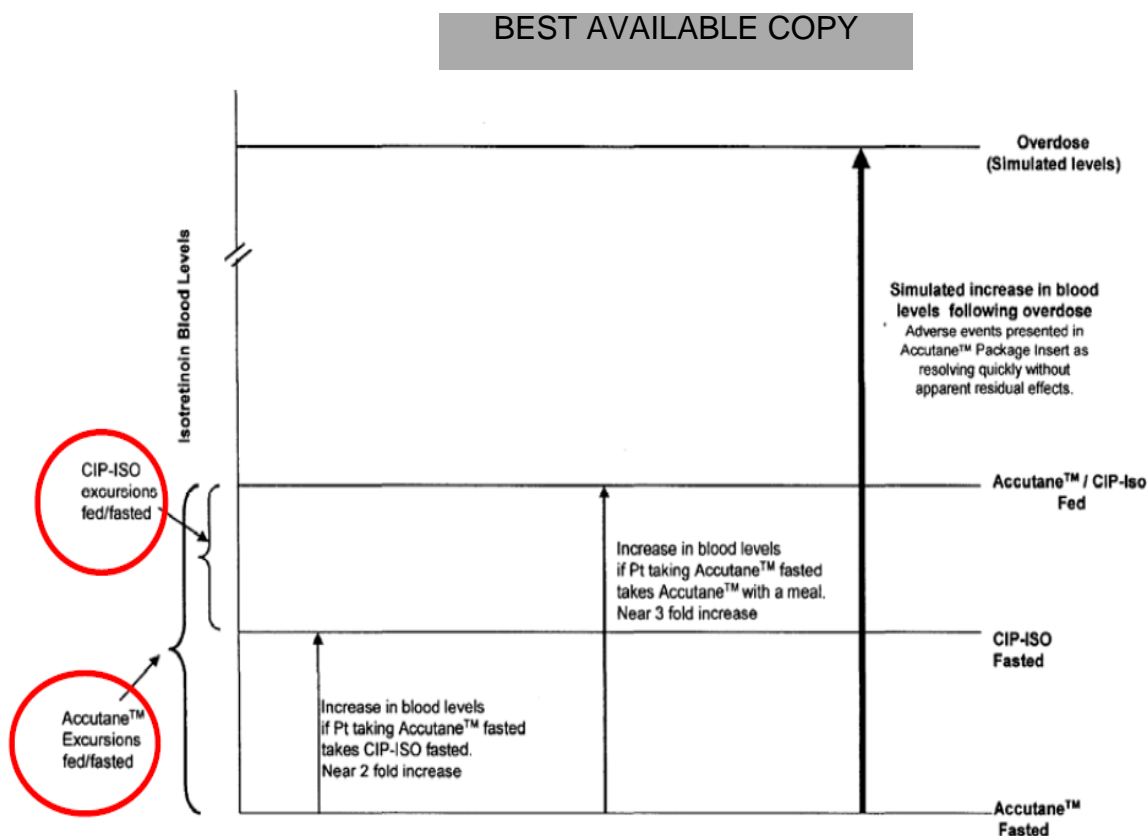
Reviewer's Comment: *Dr. Tang did not find that there were any statistically significant differences between products in terms of sub-group populations. Although the trial indicates a slight increase in efficacy in females, the reason for this is unclear, as in the analysis of drug exposure, there was no difference between males and females.*¹³

¹³ Shukla, Chinmay: Clinical Pharmacology Review, Section 2.4.1.1: Effect on gender, page 13, DARRTS 4/12/12.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dr. Chinmay Shukla reviewed the pk trials that support the dosing recommendation that cip-isotretinoin can be administered without regards to meals. The 10, 20, and 30 mg doses of cip-isotretinoin show dose proportionality and the 40 mg dose is only slightly less in dose proportionality (see explanation in section 4.4.3). Accutane[®], now generic isotretinoin, has been labeled to be taken with food since 2001 but in its initial approval in 1982 it was approved to be administered without regards to meals. Figure 3 shows a schematic of the comparative bioavailability of cip-isotretinoin to Accutane[®].

Figure 3¹⁴
Schematic Representation of the Bioavailability of Cip-isotretinoin and Accutane[®]
In the Fed and Fasted State



Reviewer's Comment: Figure 3 demonstrates that cip-isotretinoin is bioequivalent to Accutane[®] in the fed state, which is the highest bioavailability. It also shows that food has less of an effect on the bioavailability of cip-isotretinoin than on Accutane[®], as it maintains levels closer to the fed state in the fasting

¹⁴ Shukla, Chinmay: Clinical Pharmacology Review, Figure 4; page 19 in DARRTS 4/12/12.

state, than does Accutane[®] in the fasted state. Thus, as cip-isotretinoin with and without food manifests bioavailability higher than Accutane[®] fed, and Accutane[®] for 19 years was efficacious without regard to meals, I agree with Dr. Shukla in clinical pharmacology that cip-isotretinoin can be given without regards to meals and efficacy will not be compromised in the treatment of severe recalcitrant nodular acne.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This trial was not designed to evaluate persistence of efficacy or tolerance effects. Isotretinoin has been on the market for 30 years in the treatment of severe recalcitrant nodular acne. There are several articles in the literature that speak to its persistence of efficacy or lack thereof. Patients often require only a single course of treatment with isotretinoin and improvement continues even after the drug has been stopped.¹⁵ After 30 years on the market, isotretinoin can induce complete and prolong remission, with an expected cure rate of 80% to 85%.¹⁶ In one study, 69% of patients (61/88) were still virtually clear of disease an average of 9 years after completing treatment with isotretinoin, whereas of the remaining patients, 16% required further treatment with conventional antibiotics and 23% required a second course of isotretinoin.¹⁷ Finally, people in their 20s or older may relapse more frequently than adolescents with similar treatment.¹⁸

¹⁵ Berson DS, Chalker DK, Harper JC, Leyden JJ, Shalita AR, Webster GF. Current concepts in the treatment of acne: report from a clinical roundtable. *Cutis*. 2003;72(1 Suppl):5-13.

¹⁶ Merritt B, Burkhart CN, Morrell DS. Use of isotretinoin for acne vulgaris. *Pediatr Ann*. 2009;38(6):311-320.

¹⁷ Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol*. 1993;129:292-296.

¹⁸ Liu A, Yang DJ, Gerhardstein PC, Hsu S. Relapse of acne following isotretinoin treatment: a retrospective study of 405 patients. *J Drugs Dermatol*. 2008;7(10):963-966.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This submission consisted of one trial, comparing the safety of cip-isotretinoin to a currently marketed generic of Accutane[®] (reference product arm of the trial). The safety population consisted of 924 subjects, 464 on cip-isotretinoin and 460 on reference product.

Reviewer's Comment: *One patient was randomized to the RP arm but never took the drug product. Thus, the ITT population had 925 subjects but the safety population had 924 subjects.*

Categorization of Adverse Events

Adverse events were categorized by System Organ Class (SOC) and MedDRA terms.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population consisted of 924 subjects, 464 on Cip-isotretinoin and 460 on referenced product. Enrolled subjects were between the ages of 12 and 52, with 43% of the enrolled subjects < 18 years old. Approximately 60% of subjects in both arms were male, predominately white (87%) and non-Hispanic (87%). The overwhelming majority of the subjects were from the United States (81%). See section 6.1.2 for baseline demographics of the ITT population which is essentially the safety population, minus 1 subject (see comment section 7.1.1).

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 subjects (90.3%) of the safety population received treatment for at least 16 weeks, and 807/924 subjects (87.3%) received at least 19 weeks of treatment. Excluding missing data from the analysis, 837/924 subjects (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 subjects (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 (see reference 11 comment, section 5.3).

7.2.2 Explorations for Dose Response

There were no explorations to correlate drug dose or drug concentration with response. The current approved dose of isotretinoin, 0.5 mg/kg up to 2.0 mg/kg, has a long history of efficacy in this indication (see section 6.1.9).

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was done, as this application in a 505(b)(2).

7.2.4 Routine Clinical Testing

Blood for laboratory tests were collected at screening, and at weeks 4, 8, 12, 16, 20 during treatment, and at week 24, the follow-up visit for hematology, serum chemistries, and urinalysis. An additional evaluation at week 2 occurred for LFTs and for the lipid profile. Additional tests for pregnancy in females of childbearing potential was obtained at baseline (with the first dose being administered the following day) and at week 24. Hematology parameters included: red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, differential count, platelet count, and Hb-A1c (only in patients who presented with diabetes mellitus, Types I and II at Screening).

Serum chemistry parameters included: glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma-glutamyltransferase (GGT), total bilirubin, sodium, potassium, chloride, bicarbonate (HCO₃), calcium, phosphate, creatine kinase (CK), and 25-hydroxyvitamin D (at Screening only in pediatric subjects 12-17 years old and the subset of adult subjects enrolled in the bone study).

Urinalysis parameters included: pH, specific gravity, glucose, ketones, bilirubin, protein, and occult blood.

Parameters included in the lipid profile included: total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and triglycerides and were to be obtained from the subject in the fasting state (see table 4, section 5.3).

7.2.5 Metabolic, Clearance, and Interaction Workup

Not evaluated in this 505(b)(2) application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The trial was a double-blind active controlled trial in which the applicant was charged to evaluate several safety issues known to be associated with the use of isotretinoin.

These include the following:

- Prospective assessment for psychiatric and CNS events by specialists and appropriate instruments, with attention to risk factors and response to intervention
- Adequate monitoring for bone mineral density changes and premature closure of the epiphyses
- Adequate testing for hearing and vision impairment with sufficient follow-up to inform labeling regarding reversibility
- Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility

This trial did evaluate those safety issues of special concern. In addition, the trial had a sufficient number of subjects to detect adverse events which occur at an incidence of 1% of the population for safety (see **Section 7.3.5**)

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during and for 30 days after the trial (which was the follow-up period).

7.3.2 Nonfatal Serious Adverse Events

There were 12 SAEs during the course of the trial, 7 (1.5%) in the CIP group and 5 (1.1%) in the RP group. Three of the SAEs in the CIP group were considered possibly related to study med, abdominal pain (2) and migraine. None of the 5 serious events in the RP group was considered related to study med. All of the subjects in the cip-isotretinoin group recovered without sequelae. In the RP group, 4 of the 5 recovered without sequelae and 1 recovered with sequelae. There were 2 pregnancies in the trial, one in each group. Both ended in termination. See table 12.

Table 12
Subjects with Serious Adverse Events
Safety Population

Site/ Patient	Age/Race/ Gender ^a	Category/ Preferred Term/ Verbatim Term	Onset Date (Day ^b) Resolution Date (Day ^b)	Intensity	Relationship to Drug Treatment	Serious / Outcome/ Action Taken
CIP-ISOTRETINOIN			(b) (4)			
01/001	18/WH/M	Psychiatric / Substance abuse/ Substance abuse		Moderate	Not Related	Yes / Recovered / Hospitalization
11/041	17/WH/M	Injury, poisoning, procedural complications/ Ligament rupture/ Torn ACL ^c		Mild	Not Related	Yes / Recovered / Con Med, Hospitalization
13/016	14/WH/F	Gastrointestinal / Abdominal pain/ Abdominal pain		Severe	Possibly	Yes / Recovered / Con Med, Hospitalization
17/001	23/WH/F	Pregnancy, puerperium, perinatal conditions/ Pregnancy / Pregnancy		Mild	Not Related	Yes / Recovered / Discontinued from study, D&E ^c performed
34/007	14/WH/F	Gastrointestinal / Abdominal pain upper/ Stomach ache, abdominal pain		Severe	Possibly	Yes / Recovered / Hospitalization, discontinued from study
36/028	16/WH/F	Nervous system /Migraine/Migraine		Moderate	Possibly	Yes / Recovered / Con Med, Hospitalization
46/003	18/WH/M	Infections and infestations/ Orchitis/ Orchitis		Severe	Not Related	Yes / Recovered / Con Med, Hospitalization
Reference Product						
03/023	41/WH/F	General and administration site conditions Chest pain Atypical chest pain		Severe	Not Related	Yes / Recovered with sequelae / Hospitalization

Site/ Patient	Age/Race/ Gender ^a	Category/ Preferred Term/ Verbatim Term	Onset Date (Day ^b) Resolution Date (Day ^b)	Intensity	Relationship to Drug Treatment	Serious / Outcome/ Action Taken
Reference Product (continued)						
04/002	31/WH/F	Infections and infestations/ Varicella/ Chickenpox	(b) (4)	Severe	Not Related	Yes / Recovered / Con Med, Hospitalization
05/017	26/WH/F	Hepatobiliary / Cholelithiasis/ Cholecystitis with cholelithiasis	(b) (4)	Severe	Not Related	Yes / Recovered / Hospitalization, discontinued from study
28/022	19/WH/F	Pregnancy, puerperium, perinatal conditions, Pregnancy / Pregnancy	(b) (4)	Mild	Not Related	Yes / Recovered / Discontinued from study, pregnancy termination
45/027	22/WH/M	Respiratory, thoracic, and mediastinal / Asthma / Exacerbation of asthma	(b) (4)	Moderate	Not Related	Yes / Recovered / Con Med, Hospitalization

Source: [Data Listing 16.2.7.2.](#)

a: Race: WH = White; BL = Black / African American; AS = Asian; NH = Native Hawaiian or Other Pacific Islander; AI = North American Indian or Alaska Native; OT = Other.

Gender: M = Male; F = Female

b: Study day is relative to the date of first dose (Day 1)

c: Other abbreviations: ACL = anterior cruciate ligament; D&E = dilation and evacuation; .

Reviewer's Comment: For **subject 01/001**, I agree with the applicant that his problem of substance abuse, which occurred 23 days after the subject finished his course of treatment, was not related to study drug. The courts referred the subject for inpatient substance abuse treatment, which he completed and after 22 days was discharged. **Subject 13/016**, a 14 year old with a history of UTIs, had a pyelonephritis episode which required hospitalization. I do not believe that this was related to cip-isotretinoin. However, the subject had a subsequent bout of abdominal pain that resolved 2 days after the medication was stopped. This made the investigator conclude that her abdominal pain from both episodes was possibly related to cip-isotretinoin. For pregnancies see section 7.6.2.

7.3.3 Dropouts and/or Discontinuations

During the trial, 130/924 (14%) subjects discontinued treatment. Of the 70 withdrawals in the CIP group, 19 (4%) were due to an AE. Of the 60 withdrawals in the RP group, 15 (3%) were due to an AE. The most common AE that lead to discontinuation for the CIP group was psychiatric (5) and GI (5) and for the RP group it was also psychiatric (5) but musculoskeletal and connective tissue disorders was the other (4). The biggest reason for discontinuation for both arms was lost to follow-up, 20 and 16 subjects, respectively.

Reviewer's Comment: *The dropout rate between cip-isotretinoin and the reference product was similar. They were also similar in terms of drop-outs due to psychiatric events, a known concern with isotretinoin. This will be commented on further under section 7.3.5 under the psychiatric evaluation.*

7.3.4 Significant Adverse Events

Table 13 gives a summary overview of the adverse events between the two products. It shows that there was not a statistically significant difference between cip-isotretinoin and the reference product. More detail on these events, especially those of primary safety concern will be elaborated upon in subsequent sections of this review.

Table 13
Overall Summary of Adverse Events
Safety Population

	CIP-ISOTRETINOIN (N = 464)	Reference Product (N = 460)	P value ^a
Patients with Any AE, n (%)	428 (92.2)	413 (89.8)	0.2067
Number of AEs	1953	1912	
Patients with Any Treatment-related AE, n (%)	403 (86.9)	385 (83.7)	
Number of Treatment-related AEs	1494	1510	
Patients with Any Serious AE, n (%)	7 (1.5)	5 (1.1)	
Number of Serious AEs	7	5	
Patients with Any Treatment-related Serious AE	3 (0.6)	0	
Number of Treatment-related Serious AEs	3	0	
Patients with Any Severe AE, n (%)	20 (4.3)	21 (4.6)	
Number of Severe AEs	31	32	
Patients with any Treatment-related Severe AE, n (%)	12 (2.6)	17 (3.7)	
Number of Treatment-related Severe AEs	21	25	
Patients with any AE Leading to Study Discontinuation, n (%)	19 (4.1)	15 (3.3)	0.6009
Patients with AEs by MedDRA SOC:			
Psychiatric, n (%)	29 (6.3)	27 (5.9)	0.8905
Eye ^b , n (%)	144 (31.0)	135 (29.3)	0.6160
Ear and Labyrinth, n (%)	10 (2.2)	10 (2.2)	1.0000
Musculoskeletal and Connective Tissue, n (%)	174 (37.5)	172 (37.4)	1.0000
Vascular, n (%)	4 (0.9)	4 (0.9)	1.0000
Cardiac, n (%)	2 (0.4)	3 (0.7)	0.6855
Gastrointestinal ^c , n (%)	60 (12.9)	52 (11.3)	0.4811

Source: NDA 21-951: Final Study Report, table 12-3 page 133.

7.3.5 Submission Specific Primary Safety Concerns

Over the 30 years that isotretinoin has been marketed, there have developed safety issues of primary concern. As stated earlier in the review, in the approvable letter, the applicant was asked to evaluate with their drug a comparative trial focusing on the

following known safety issues with isotretinoin: neuropsychiatric, bone, hearing, and vision. Each of these evaluations was consulted to the respective divisions to be reviewed. The summary of the findings for each safety concern will be presented below. The reader is referred to each review for further details.

Neuropsychiatric Evaluation

Previous neuropsychiatric events were observed in study 442, a biopharmaceutics trial submitted in the original NDA July 1, 2005, which precipitated the necessity to have trial ISOCT.08.01 conducted. Briefly, study 442, was an 11-day multi-dose, in house trial in 36 subjects, comparing different doses of cip-isotretinoin to Accutane in healthy subjects.¹⁹ In this trial, subjects were taking cip-isotretinoin 30 mg q day with food or Accutane 40 mg q day with food. In that trial, there were 7 total neuropsychiatric events, 6 on the cip-isotretinoin arm and 1 on the Accutane arm. Three subjects on the cip-isotretinoin arm experienced euphoria and 1 on the Accutane arm. A total of 3 discontinuations occurred because of neuropsychiatric events in trial 442, all on the cip-isotretinoin arm and are elucidated in table 14.²⁰

Table 14
Neuropsychiatric Events Resulting in Discontinuation
Trial 442⁸

Drug	Patient #	Adverse Event
Cip-Isotretinoin 30 mg QD	6	Emotional labile; agitation; insomnia; less social; punched walls which resulted in swollen hands and necessitated a hospital visit; cleared by psych
	13	Irritation and "momentary" (91 hours) desire (rage) to hurt people
	26	Non-compliance; agitated; threw food in garbage on day 8; euphoria; weakness
Accutane 40 mg QD	No discontinuations because of adverse events	

Source: NDA 21-951, Module 5, Volume 1.138; Module 5 section 3, page 34, submitted 7/1/2005.

The evaluation of cip-isotretinoin compared to reference product for trial ISOCT.08.01 was reviewed by Gregory Dubistky, M.D. in the Division of Psychiatry Products. A summary is provided below and the reviewer is referred to the complete review in DARRTS, dated 2/27/12.

In this trial, psychiatric monitoring was evaluated 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.

¹⁹Denise Cook, M.D.: Medical Officer Review, NDA 21-951, page 9: DARRTS- 4/27/2006.

²⁰Denise Cook, M.D.: Medical Officer Review, NDA 21-951, page 10: DARRTS – 4/27/2006.

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 was based on responses to three questions.

All patients had baseline psychiatric evaluations. The percentage of subjects with a previous psychiatric history was fairly evenly distributed between the 2 arms. In the cip-isotretinoin arm 11.6% of patients had a history of psychiatric disorder compared to 13.9% in the reference product arm. There was also no major difference in psychiatric drug use between the two randomized groups.

Psychiatric adverse reactions were fairly equal in both arms, reported in 6.3% (29/464) of subjects in the cip-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 CIP 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 CIP group and 4 (0.9%) for the RP group. However, according to one of the assessments, 2 subjects in the CIP group had ongoing depression that predated the trial. One psychiatric adverse event was 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."

Ten subjects, 5 in each group withdrew from the trial due to psychiatric events. 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.

As stated above, 4 tools were used during the trial to assess psychiatric events. Using the **PHQ-8**, 4 subjects on cip-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 cip-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 cip-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.

Reviewer's Comment: *In summary, although there was a signal in the biopharmaceutics trial 442, that showed an increase in psychiatric events in subjects*

taking cip-isotretinoin as compared to Accutane, trial ISOCT.08.01, which compared the two drugs at the same dosages over 20 weeks of therapy did not demonstrate any significant difference in terms of neuropsychiatric events between these two drug products. In labeling, under clinical trials experience for psychiatric events, irritability, anger, emotional instability, euphoria, and violent behavior will be added under TRADENAME, as they were observed in >1% of subjects in trial 442.

Bone Evaluation

The evaluation of cip-isotretinoin compared to reference product was reviewed by Stephen Voss, M.D. in DRUP. The reader is referred to his complete review in DARRTS dated 4/10/12. His summary and conclusion of the findings are as follows:

“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=.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 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 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 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. (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 older adolescents. Though there were somewhat more CIP-Isotretinoin subjects with BMD decline in the 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 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 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 ~ 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 ≥ 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 adult 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.

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.²¹

Reviewer's Comment: *I agree with Dr. Voss, that this trial confirmed the already known findings of isotretinoin's effect on BMD that was discovered in a previous adolescent trial and while a few more individuals were affected in the cip-isotretinoin arm as compared to the reference product, the two drug products are not significantly different in their effect on bone. This trial also looked at other parameters to try to assess if one could tell who might be at risk for the adverse effects on BMD but none were discovered.*

There were 27 adolescent subjects who experienced BMD loss at either the total hip or femoral neck or both and the population affected here were primarily boys with a mean age of about 14.8 years. At this age the mean annual increase in bone mineral density for the total hip and femoral neck in boys is 3.4%-8.6% and 3.5%- 6.6% depending on age, with the higher percentage occurring in the younger adolescent. For the mean age of boys in this trial with bone loss, the mean annual increase would be about 8% and 6%, respectively for total hip and femoral neck.²² Thus, after 5-6 months of therapy, there should have been an increase of approximately 4% in the total hip BMD and 3% in the femoral neck. This did not occur in this trial. The trial did present an opportunity to determine if these adverse effects were long-term or whether BMD could be recovered,

²¹ Consult Review: Review of Bone Safety Data: Stephen Voss, M.D., DRUP: pgs. 25-27, DARRTS 4/10/12.

²² Consult Review: Review of Bone Safety Data: Stephen Voss, M.D., DRUP: pgs. 12 & 15, DARRTS 4/10/12.

but unfortunately, the applicant did not comply with the Agency's request. I agree with Dr. Voss that this must be addressed in labeling (see section 9.2).

Audiology Evaluation

The evaluation of cip-isotretinoin compared to reference product (marketed generic isotretinoin) was reviewed by James Kane, PHD in CDRH. The reader is referred to his complete review dated 2/28/12. His summary and conclusion of the findings are as follows:

Adverse events were reported by 2.2% of subjects in both the cip-isotretinoin arm and in the reference product arm. The highest of these was ear pain occurring in 3 subjects each and hypoacusis, 3 in the cip-isotretinoin arm and 2 in the reference product arm.

A total of 180 subjects at 10/49 centers (20.4%)²³ in the United States and Canada underwent audiology testing: 86 subjects in the cip-isotretinoin arm and 94 in the reference product arm. Two (2.3%) subjects in the cip-isotretinoin arm and 5 (5.3%) in the reference product arm experienced a threshold shift in either ear. This difference was not statistically significant.

Dr. Kane concludes that the safety results from this evaluation for audiology changes in this trial are consistent with what was accepted for the approved drug Accutane. However, because of the small sample size of only 19% of subjects, he is not convinced that the results from this small sample size is sufficient to generalize the results to the overall study population or even to the general indicated population. He does admit, though, that because the reported threshold shifts for those subjects evaluated was low and in the absence of a significant difference between the two subject arms, it suggests that cip-isotretinoin is no worse than the already marketed isotretinoin.

Reviewer's Comment: *I agree with Dr. Kane that it would have been more informative if all subjects had been assessed for audiology changes. However, in the absence of that and given that the primary objective was to detect a difference in the two drug products, I feel that examining a subset of subjects and finding no difference is sufficient to say that use of cip-isotretinoin does not present an increase safety concern over the currently marketed generics of Accutane® in terms of hearing changes. There were also only a small percentage of subjects that reported adverse events concerning hearing and no difference between the two products was observed for reported adverse reactions.*

Ophthalmology Evaluation

The evaluation of cip-isotretinoin compared to reference product was reviewed by William Boyd, M.D. in DTOP. Dr. Boyd completed 2 reviews. The first one states that

²³ On my review of the datasets, 10 study sites, 8 in the US and 2 in Canada conducted audiology testing: sites 04, 05, 07, 10, 17, 22, 27, 37, 40, and 45.

the ophthalmology assessments were not evaluated correctly by the applicant and needed to be resubmitted with specific evaluations requests by the Division. The 2nd review gives the results of Dr. Boyd's evaluation of the second presentation by the sponsor. The reader is referred to his complete reviews in DARRTS, the first dated 2/21/12 and the second dated 4/9/12. The following summary and conclusion reflect Dr. Boyd's second review.

Subjects were tested for visual acuity changes over time during each visit of the trial up to and including week 24. Dr. Boyd did not find any significant differences between drug products. Overall, 20 (4.3%) subjects in the cip-isotretinoin arm experienced a reduction in visual acuity compared to 25 (5.4%) in the reference product arm.

In terms of eye adverse reactions, there were no significant differences between the cip-isotretinoin arm and the reference product arm. There were 2 subjects that discontinued the trial on the cip-isotretinoin arm, one due to night blindness and one due to punctate keratitis. Dr. Boyd did an evaluation of the narrative summaries for subjects that had AEs that affected vision and found that protocol mandated referral to an ophthalmologist and request for ERG was arbitrary and inconsistent.

In summary, Dr. Boyd found that because this protocol did not provide adequate ocular monitoring of study subjects, the ocular safety of the study treatments were not adequately addressed. Thus, specific reference to the ophthalmologic findings of this clinical trial (ISOCT.08.01) was recommended to be eliminated from the proposed labeling for the drug product by DTOP. Further, that the general statements regarding isotretinoin products found in Section 5.13 and throughout the package insert and patient package insert should be retained.

Reviewer's Comment: *While the protocol did not provide for adequate ocular monitoring of study subjects, the monitoring that did occur did not find any significant differences between cip-isotretinoin and a marketed generic of Accutane[®] in terms of increased ocular risk with cip-isotretinoin. The trial did not reveal any new ocular findings for either drug. I agree with Dr. Boyd that the general statements regarding ocular findings in the generic isotretinoin labeling should be retained for cip-isotretinoin.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 15 lists the common adverse events that occurred in trial ISOCT.08.01

Table 15
Adverse Events Occurring in ≥5% of Patients
Safety Population

	CIP-ISOTRETINOIN (N = 464)	Reference Product (N = 460)
Patients with Any AE, n (%)	428 (92.2)	413 (89.8)
Lip dry	209 (45.0)	210 (45.7)
Dry skin	205 (44.2)	206 (44.8)
Back pain	96 (20.7)	89 (19.3)
Dry eye	87 (18.8)	78 (17.0)
Arthralgia	64 (13.8)	60 (13.0)
Epistaxis	54 (11.6)	42 (9.1)
Headache	37 (8.0)	36 (7.8)
Nasopharyngitis	36 (7.8)	48 (10.4)
Chapped lips	34 (7.3)	32 (7.0)
Dermatitis	28 (6.0)	23 (5.0)
Blood creatine kinase increased ^a	26 (5.6)	27 (5.9)
Cheilitis	26 (5.6)	19 (4.1)
Musculoskeletal discomfort	25 (5.4)	16 (3.5)
Upper respiratory tract infection	25 (5.4)	14 (3.0)
Visual acuity reduced	23 (5.0)	25 (5.4)

^aBlood creatine kinase increased - In this category, this reflects investigator's who listed the increase as an adverse event. This does not reflect the total number of subjects with elevations in the trial.

Source: NDA 21-951: Final Study Report – table 12-4, page 136.

The majority of subjects in both arms experienced an adverse event, 92% in the cip-isotretinoin arm and 90% in the reference product arm. Evaluation of AEs by maximum intensity showed that the majority of subjects only experienced mild AEs (55% vs. 53% in the CIP and RP 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 CIP and 21 (5%) of subjects in the RP group.

Laboratory Findings

A high frequency of abnormal laboratory values was reported in both treatment groups. The most frequently reported abnormalities in both treatment groups were elevated CK

levels, with high alert values being reported for 30% of subjects in the CIP group and 28% of subjects in the RP group, by the applicant's analysis. Elevated liver function enzymes (ALT, AST, and GGT) were also reported with high frequency as were increases in serum triglycerides. 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 study in both groups. Shifts to above the normal range were noted for more than 10% of the subjects in one or both treatment groups for the following variables (listed by frequency for cip-isotretinoin vs. reference product group, respectively): triglycerides (21% vs. 18%), LDL cholesterol (14.5% vs. 18%), cholesterol (14% vs. 15%), CK (11% vs. 12%), and glucose (11% vs. 9%). This was the applicant's analysis. Table 16 shows this reviewer's analysis from the data sets submitted to the NDA by the applicant. In this table, any subject with an isolated elevation at baseline or an isolated elevation at follow-up was not included and any subject who had both an 'H' and 'HH' value during the trial was only counted as 'HH'.

Table 16
Shifts to Above Normal Range in > 10% of Subjects
Safety Population

	CIP (N=464)		Reference Product (N=460)	
	# of Subj. with "H" ¹ (%)	# of Subj. with "HH" ¹ (%)	# of Subj. with "H" ¹ (%)	# of Subj. with "HH" ¹ (%)
Triglycerides	160 (34)	0	160 (38)	0
Cholesterol	181 (39)	0	162 (35)	0
LDL Cholesterol	132 (28)	0	150 (33)	0
Creatine Kinase	159 (34)	111 (24)	160 (35)	104 (23)
Glucose	155	0	148	0
¹ H = high; HH= high alert (≥350 U/L) Source: NDA 21-951: SAS Dataset "lb.xpt."				

Reviewer's Comment: *Of these laboratory values where more than 10% of subjects shifted to high, for the CK where there were also high alerts, the total together was essentially the same for cip-isotretinoin and reference product, 270/464 (58%) and 264/460 (57%), respectively.*

Laboratory values were presented by the applicant in 3 ways, those that were flagged by the reporting laboratory as a high alert, those that were identified as clinically significant by the investigator, and those that were reported as an adverse event by the investigator. In all 3 evaluations, there was not much of a difference between cip-isotretinoin and the reference product. Table 17 shows the laboratory values that were marked as high alert.

Table 17
High Alert Laboratory Values, n/N (%) of Patients
Safety Population

Laboratory Variable	CIP-ISOTRETINOIN (N = 464)	Reference Product (N = 460)
ALT	5/464 (1.1)	8/460 (1.7)
Alkaline phosphatase	0	1/460 (0.2)
AST	4/464 (0.9)	8/460 (1.7)
Creatine kinase	138/464 (29.7)	128/460 (27.8)
GGT	9/464 (1.9)	9/460 (2)
Potassium	3/464 (0.6)	1/460 (0.2)

Source: NDA 21-951: Final Study Report table 12-23, page 180.

Reviewer's Comment: *The high alert CK (flagged HH) from the sponsor differs from my analysis of the data sets (see table 16). Even so, the difference between the products is not significant. The marked elevation (flagged HH and listed as CK ≥ 350 U/L) in CK is additional information that would be useful in labeling. I will recommend that my analysis from the datasets is used, that is: marked elevation (CK ≥ 350 U/L) was seen in 24% of subjects using TRADENAME.*

Table 18 shows the laboratory values that were considered clinically significant at some time point during the trial by the investigator in ≥ 1% of subjects. These are identified with an asterisk (*) in the data listings of clinical laboratory results but may not have met the criteria for as low or high alert nor were they always reported as AEs.

Table 18
Laboratory Values Noted as Clinically Significant by Investigator
In ≥ 1% of Patients (Any Group)
Safety Population n (%)

	Cip- Isotretinoin N= 464	Reference Product N=460
Clinically Significant Laboratory Values - Chemistry		
Creatine kinase	20 (4.3)	17 (3.7)
AST	19 (4.1)	12 (2.6)
ALT	13 (2.8)	12 (2.6)
Bicarbonate	9 (1.9)	5 (1.1)
GGT	7 (1.5)	12 (1.1)
Bilirubin	7 (1.5)	5 (1.1)
Glucose	7 (1.5)	4 (0.9)
Alkaline phosphatase	5 (1.1)	1 (0.2)
Clinically Significant Laboratory Values - Lipids		
Triglycerides	9 (1.9)	8 (1.7)
Cholesterol	5 (1.1)	5 (1.1)
HDL Cholesterol	5 (1.1)	4 (0.9)
Clinically Significant Laboratory Values - Hematology		
Lymphocytes	15 (3.2)	17 (3.7)
Leukocytes	11 (2.4)	11 (2.4)
Monocytes	8 (1.7)	2 (0.4)
Eosinophils	7 (1.5)	9 (2)
Neutrophils	6 (1.3)	10 (2.2)
Hematocrit	5 (1.1)	6 (1.3)
Source: NDA 21-951: Final Study Report, page 182-183 .		

Reviewer's Comment: *The labs flagged as clinically significant by the investigator are smaller than the number of subjects reported to have elevations of laboratory values. Table 19 will show that the number of laboratory abnormalities that were reported as adverse events is even smaller. This cannot be reviewed, as the applicant did not provide any narratives or CRFs for these subjects.*

Table 19
Laboratory Values Reported as AEs ≥ 1% of Patients (Any Group)
Safety Population

	Cip- Isotretinoin N= 464	Reference Product N=460
Blood creatine kinase	26 (5.6)	27 (5.9)
Blood triglycerides	17 (3.7)	14 (3.0)
Alanine aminotransferase increased	10 (2.2)	11 (2.4)
Aspartate aminotransferase increased	8 (1.7)	10 (2.2)
Gamma-glutamyltransferase increased	3 (0.6)	5 (1.1)
Source: NDA 21-951: Final Study Report, adapted from table 12-24, page 181.		

Severe increases in CK were seen in 3 subjects in the Cip-isotretinoin group (pts 08/019, 12/008, and 12/014). Subject 08/019, an 18 year old White male, had a normal CK at week 4. At week 8, the CK had risen to 797 (and listed as a high alert but not clinically significant). At an unscheduled visit 2 weeks later, the CK was down to 100 and remained in the normal range for the remainder of the trial, with it at 78 at week 24. Subject 12/008, an 18 year old white male had a screening CK of 119. At week 8, his CK rose to 567 (listed as a high alert but not clinically significant). At week 12, the CK had fallen to 91 and remained normal for the duration of the trial and at week 24 was back at his baseline of 119. Subject 12/014 was a 24 y/o white male with a screening CK of 96 and 25-hydroxyvitamin D level of 14 (which was low). His CK rose to 1371 (clinically significant) at week 4 but had fallen to normal at week 8 with a value of 108. It rose again over the next month to 630 (a high alert but not clinically significant) before falling again at week 20 to 125 and by week 24 it was 112.

Reviewer's Comment: *The applicant did not provide any clinical narratives or CRFs for these subjects, so there is no clinical correlation to the high laboratory values for these subjects. However, all 3 of the subjects had only transient elevations at different time points during the trial and all were normal by week 24, end of follow-up. Table 20 also shows that mean CK values showed a downward trend by week 24. This is consistent with current isotretinoin labeling and the literature.*

Table 20
CK Values (u/L) over Time
Actual Value and Change from Baseline

	Cip-Isotretinoin N=464		Reference Product N=460	
	Actual Value	Change from BL	Actual Value	Change from BL
Baseline (BL)				
N	463		460	
Mean (SD)	158.9 (261.8)		139.9 (111.1)	
Min, Max	30, 4828		38, 1099	
Week 2				
N	11	11	3	3
Mean (SD)	165.5 (115.8)	24.6 (114.7)	101.7 (40.8)	-27 (48.2)
Min, Max	31, 465	-86, 341	68, 147	-81, 12
Week 4				
N	443	442	449	449
Mean (SD)	181.9 (336.5)	22.7 (398.7)	174.4 (370.8)	34.1 (377.6)
Min, Max	26, 6281	-4612, 5829	32, 7313	-828, 7726
Week 8				
N	437	436	436	436
Mean (SD)	159.5 (165.1)	-1.38 (286.3)	194.6 (478.4)	53.7 (461)
Min, Max	28, 1570	-4611, 1310	19, 7563	-688, 7293
Week 12				
N	424	423	422	422
Mean (SD)	184.0 (394.5)	23 (457)	159.5 (236.3)	19.2 (242.2)
Min, Max	35, 7261	-4459, 7128	37, 4256	-866, 4200
Week 16				
N	414	413	415	415
Mean (SD)	162.5 (172)	2.07 (295)	162 (182)	19.6 (192)
Min, Max	30, 1995	-4558, 1861	36, 2031	-873, 1942
Week 20				
N	402	401	408	408
Mean (SD)	247.5 (1317)	85.9 (1343)	186.6 (416)	46.1 (417.7)
Min, Max	32, 2593	-4679, 25812	33, 6751	-846, 6597
End of Treatment				
N	454	453	456	456
Mean (SD)	234 (1240)	75.3 (1264)	179.8 (395.6)	39.3 (398)
Min, Max	31, 25936	-4679, 25812	19, 6751	-846, 6597
Week 24				
N	396	395	403	403
Mean (SD)	185.6 (283)	21.7 (379)	190.9 (404)	47.5 (410)
Min, Max	26, 3610	-4685, 3275	29, 5732	-900, 5667

Source: NDA 21-951: Final Study Report, adapted from post-text table 14.4.1.2, pages293-296

It is well known that isotretinoin adversely affects the lipid profile in patients who take the drug. The following analysis by this reviewer shows that almost all subjects have some increase in the lipid levels of triglycerides, LDL cholesterol, and total cholesterol and a decrease in the HDL cholesterol from their own baseline (see tables 21 and 22). Approximately half of these subjects return to their own baseline by the end of the trial

(4 weeks post treatment). The tables also show that there is basically no difference between cip-isotretinoin and reference product in the effect on lipid metabolism.

Table 21
Analysis of Lab Data for Triglycerides, Cholesterol and LDL Cholesterol
Safety Population

	CIP (N=464)		Reference Product (N=460)	
	# of Subj. with elevation	# of Subj. returned to baseline	# of Subj. with elevation	# of Subj. returned to baseline
Triglycerides	419	262	421	259
Cholesterol	405	261	414	256
LDL Cholesterol	418	293	430	295

Source: NDA 21-951: Sas Datasets adlb.xpt and adlbsft.xpt and Appendix 16.2.8.4, pages 1-231.

Table 22
Analysis of Lab Data for HDL Cholesterol
Safety Population

	CIP (N=464)		Reference Product (N=460)	
	# of Subj. decreased	# of Subj. returned to baseline	# of Subj. decreased	# of Subj. returned to baseline
HDL Cholesterol	424	361	413	312

Source: NDA 21-951: Datasets adlb.xpt and adlbsft.xpt and Appendix 16.2.8.4, pages 1-231.

Reviewer's Comment: *In summary, analysis of the laboratory data did not reveal any significant differences between cip-isotretinoin and the reference product. Overall, the means for these laboratory abnormalities trended towards normal by the end of the trial, the 4 week follow-up. Only 3 subjects, all in the cip-isotretinoin arm (0.6%) discontinued because of a laboratory abnormality. That does not represent a significant difference over the reference product. As marked elevations of CK are not commented upon in the present labeling of currently marketed isotretinoin, it will be useful to add it to the cip-isotretinoin labeling. Laboratory abnormalities will be in the labeling and it will be left to the doctor to correlate the abnormality with the overall clinical presentation of the individual patient.*

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in this trial.

7.4.5 Special Safety Studies/Clinical Trials

This complete response only contained one comparative clinical trial. No special safety studies were performed in addition to this trial.

7.4.6 Immunogenicity

Immunogenicity was not evaluated in this trial.

7.5 Other Safety Explorations

There were no other safety explorations.

7.5.1 Dose Dependency for Adverse Events

This trial did not reveal any new dose dependency for adverse events for the moiety, isotretinoin. There was no titration, other than 0.5 mg/kg/day for the 1st four weeks. For the latter 16 weeks, the dose was 1 mg/kg/day.

7.5.2 Time Dependency for Adverse Events

No formal evaluations were done in this trial for time dependency for adverse events. However, given that the overall analysis of safety does not reveal any significant difference between cip-isotretinoin and a generic of Accutane[®], any established time dependency for adverse events for Accutane[®] should be the same for cip-isotretinoin.

7.5.3 Drug-Demographic Interactions

See section 7.3.5 (Bone Evaluation) where differences in bone mineral density changes between adult and pediatric subjects and male and female subjects are discussed.

7.5.4 Drug-Disease Interactions

No formal evaluations for drug-disease interactions were evaluated in this trial. The drug-disease interactions for isotretinoin are well elucidated in the labeling for isotretinoin, and cip-isotretinoin will have the same labeling.

7.5.5 Drug-Drug Interactions

No formal evaluations for drug-drug interactions were evaluated in this trial. The drug-drug interactions for isotretinoin are well elucidated in the labeling for isotretinoin, and cip-isotretinoin will have the same labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no known association of isotretinoin with carcinoma in humans.

7.6.2 Human Reproduction and Pregnancy Data

There were 2 pregnancies in the clinical trial, one in the cip-isotretinoin arm and one in the reference product. Both pregnancies ended in termination.

Subject **17/001** was a 23 y/o white female on orthotricyclen for oral contraception. The subject was counseled appropriately on needing 2 forms of contraception for this trial. Her second form of contraception was male condom with spermicide, which she was using for one month prior to randomization. Pregnancy occurred (b) (4) after being on study medication *cip-isotretinoin) at visit 4. Patient voluntarily elected termination of the pregnancy which occurred on (b) (6) and subsequent termination visit revealed a negative pregnancy test.

Subject 28/022 was a 19 year old white female on Loestrin 24 for oral contraception and male latex condom as the secondary form of contraception. The subject was counseled regarding contraception as per protocol. On study visit 8, patient was pregnant but had been negative at all previous study visits and claimed to be using both forms of contraception throughout the trial. Medication had been stopped by the patient a few days prior to visit 8. The subject elected to terminate the pregnancy.

Reviewer's Comment: *In my opinion, these 2 pregnancies were not due to a lack of the investigator to follow protocol but was either contraceptive failure or non-compliance.*

Isotretinoin is a human teratogen and is distributed under a REMS called iPLEDGE. Cip-isotretinoin will participate in the same REMS program once marketed.

7.6.3 Pediatrics and Assessment of Effects on Growth

PREA does not apply to this application because the proposed indication, active ingredient, dosage form, dosing regimen and route of administration are the same as for the listed drug.

See section 7.3.5 for effects on growth (Bone Evaluation).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The clinical trial did not evaluate for this. There is no known overdose, drug abuse potential, withdrawal or rebound with over 30 years marketing experience with isotretinoin. The labeling concerning drug overdose will be the same as for generic isotretinoin.

7.7 Additional Submissions / Safety Issues

There were no additional significant submissions or safety issues. The applicant submitted a safety update on 4/12/12 stating that they had no additional data to report, as the clinical trial had ended when they submitted the resubmission.

8 Postmarket Experience

There is no post marketing experience for this drug product.

9 Appendices

9.1 Literature Review/References

Berson DS, Chalker DK, Harper JC, Leyden JJ, Shalita AR, Webster GF. Current concepts in the treatment of acne: report from a clinical roundtable. *Cutis*. 2003; 72(1 Suppl):5-13.

Merritt B, Burkhart CN, Morrell DS. Use of isotretinoin for acne vulgaris. *Pediatr Ann*. 2009; 38(6):311-320.

Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol*. 1993; 129:292-296.

Liu A, Yang DJ, Gerhardstein PC, Hsu S. Relapse of acne following isotretinoin treatment: a retrospective study of 405 patients. *J Drugs Dermatol*. 2008; 7(10):963-966.

9.2 Labeling Recommendations

The following are the major clinical labeling recommendations for the cip-isotretinoin labeling. The following labeling is that which was last submitted by the applicant on 3/16/12. Changes in the labeling are denoted by ~~strikeout~~ for deletions of the applicant's proposed wording and underline for recommended additions. Cip-isotretinoin is referred to as TRADENAME throughout, as a trade name for the product is pending, as of the closure of this review.

(b) (4)

Reviewer's Comment: Section 17, "Patient Counseling Information" was updated to reflect the changes made in the body of the labeling.

9.3 Advisory Committee Meeting

No advisory committee meeting was held concerning this NDA.

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/s/

DENISE COOK
04/23/2012

GORDANA DIGLISIC
04/23/2012

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11,114**

Consultant Reviewer:	Gwen L. Zornberg, M.D., Sc.D. Medical Team Leader DPP HFD-130
Consultation Requestor:	Nichelle Rashid DDDDP HFD-540
Date of Request:	February 17, 2009
Date Received:	February 19, 2009 (Due 6 March 2009)
Date Reviewed:	March 5, 2009
Subject:	CIP-Isotretinoin (10, 20, 30 mg) Capsules

I. Background

NDA 21-951, CIP-Isotretinoin Capsules for treatment of severe recalcitrant nodular acne, received an approvable action on 25 April 2007. The Agency had 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 11 January 2008. The protocol ISOCT.08.01 entitled: "A Double-Blind, Randomized, Phase III, Parallel Group Study Comparing the Efficacy and Safety of CIP-Isotretinoin to the Marketed Formulations of Isotretinoin in Patients with Severe Recalcitrant Nodular Acne" had been submitted initially for SPA on 4 July 2008 to the Division of Dermatologic and Dental Drug Products (DDDDP). In response to Agency comments, the sponsor submitted a revised protocol on 17 February 2009 in response to recommendations by DDDDP, including consultative recommendations by the Division of Psychiatry Products (DPP) and Office of Surveillance and Epidemiology (OSE) in the interest of optimizing patient safety, particularly with regard to symptoms of suicidal behavior and ideation, as well as depressed mood. A summary of the proposals for neuropsychiatric measures is described in detail in the DPP reviews of Dr. Greg Dubitsky (30 January 2008) and Dr. Victor Crentsil (8 August 2008). Dr. Mosholder of OSE also provided consultative review (2 April 2008) to DDDP to help reduce suicide risk during the conduct of the trial.

II. Review of the Amended Protocol ISOCT.08.01

The undersigned attended the 6 August 2008 meeting held by DDDP with Cipher accompanied by experts in the field of psychiatric rating scales, Drs. Janet Williams and

Kelly Posner. The panoply of neuropsychiatric instruments considered by Cipher over the development of the study protocol to monitor symptoms of suicidality and depression were discussed in depth. Agreement was achieved on the selection of the key measures of neuropsychiatric treatment emergent symptoms for screening and during the trial.

For psychiatric diagnostic evaluation, it was agreed that the SCID and the MINI-Plus are both adequate instruments. There was also agreement that use of the Patient Health Questionnaire-8 (PHQ-8) would be adequate for the assessment of symptoms of depressive disorder as well as monitoring for changes in severity of depression symptoms over time. No objection was raised to employ in the trial the PHQ-8 (absent the suicide item) in place of the Beck Depression Inventory to monitor symptoms of depression.

It was also agreed that the C-SSRS (Columbia Suicide Severity Rating Scale), which maps to C-CASA (Columbia Classification Algorithm for Suicide Assessment) to detect the emergence of and change in the full spectrum of symptoms of suicidal behavior and ideation at each of the 9 planned study visits including the week 24, post-treatment study follow-up visit administered every time the PHQ-8 is employed-- with the exception of one study visit at week 2 of double blind treatment. As was agreed in the meeting with the applicant, as the suicide item of the PHQ-9 is redundant with and more limited than the C-SSRS, it was considered more efficient to revise the PHQ-9 scale to the PHQ-8 (absent the suicide item) to evaluate for emergence of or changes in severity of depressive symptoms.

In response to the recommendations of DDDP, protocol ISOCT.08.01 entitled: “A Double-Blind, Randomized, Phase III, Parallel Group Study Comparing the Efficacy and Safety of CIP-Isotretinoin to the Marketed Formulations of Isotretinoin in Patients with Severe Recalcitrant Nodular Acne” was revised to incorporate the DDDP recommendations and submitted for review.

III. Comments Regarding New DPP Policy for Suicidality Assessment

There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how to address this issue.

All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development. An acceptable instrument would be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). Consequently, as discussed at the 6 August 2008 meeting, the Columbia Suicide Severity Rating Scale (C-SSRS) is an acceptable instrument. For this protocol, we recommend that these assessments would need also to be included at every planned visit to adequately evaluate for suicide risk.

IV. Conclusions and Recommendations

Based on my review of the revised Phase 3 protocol ISOCT.08.01, a double-blind, randomized trial evaluating the efficacy and safety of CIP-Isotretinoin for the treatment of severe recalcitrant nodular acne, I recommend to the Division Director that Cipher has in principle responded satisfactorily to our recommendations to optimize patient safety in the trial pertaining to suicide risk. The SCID-CT is a reasonable psychiatric diagnostic instrument to identify major psychoses for exclusion from the study population. The C-SSRS and the PHQ-8 are adequate rating instruments for symptoms of suicide and depression. However, while the re-submitted protocol reads that these rating scales are to be administered at each of the 9 planned study visits, but not at the week 2 visit. It is recommended that the C-SSRS and PHQ-8 assessments would need to be administered at every planned visit of this protocol, including the week 2 study visit.

From the psychiatric standpoint, once the protocol is amended to administer the C-SSRS to evaluate for risk of suicidality at all visits during the trial (coupled with the PHQ-8 to evaluate for other symptoms of depression), this study protocol for the treatment of severe recalcitrant nodular acne will be considered safe to proceed.

Gwen L. Zornberg, M.D., Sc.D.
Lead Medical Officer
March 5, 2009

cc: NDA #21-951
HFD-540/NRashid
HFD-130/GZornbegr
/MMathis
/TLaughren
/DBerman

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Gwen Zornberg
3/5/2009 09:20:49 PM
MEDICAL OFFICER

Thomas Laughren
3/7/2009 10:05:26 AM
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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[®]), 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[®] (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[®] (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[®] 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[®] 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 ≥ 20 – severe major depression. To monitor treatment of depression, a ≥ 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[®] 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[®] 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® 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 ≥ 15 or a score of ≥ 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.

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4. Gilbody S, Richards D, Bradley S, Hewitt C (2007): Screening for depression in medical settings with the patient health questionnaire (PHQ): A diagnostic meta-analysis. J Gen Intern Med 22(11): 1596-602
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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
V. Crentsil
G. Zornberg
M. Mathis
T. Laughren
J. Lindstrom
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/s/

Victor D Crentsil
8/25/2008 05:26:52 PM
MEDICAL OFFICER

Gwen Zornberg
8/25/2008 05:42:18 PM
MEDICAL OFFICER
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

**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.¹ 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

¹ 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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1/30/2008 01:34:41 PM
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DIVISION DIRECTOR MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH OFFICE OF NEW DRUGS/ODE III DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

Date: 24April07

FROM: Susan J. Walker, M.D.
Division Director
Dermatology and Dental Products

TO: NDA 21-951

SUBMISSION: 26October06

APPLICANT: Cipher Pharmaceuticals, Ltd.

USAN NAME: Isotretinoin

TRADENAME: CIP-Isotretinoin

INDICATION: Severe recalcitrant nodular acne

SUBJECT: Decisional Memorandum

Background:

The current submission dated 26October06 is a response to the agency's "approvable" action for Cipher Pharmaceutical's original new drug submission (NDA) 21-951 dated June 27, 2005 and received July 1, 2005. This application is submitted pursuant to section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and proposes approval of Cipher's isotretinoin product based upon bioequivalence comparisons to the listed drug, Accutane®. Cipher proposes the use of CIP-Isotretinoin 10, 20, and 30mg capsules at a total daily dose of 0.5-2mg/kg/day divided into twice daily dosing for the treatment of patients 12 years and above diagnosed with severe recalcitrant nodular acne. The CIP-Isotretinoin product is intended to deliver consistent systemic bioavailability independent of food intake. In contrast, the listed isotretinoin product (Accutane®) has marked variation in systemic bioavailability depending upon the fed/fasted state, and is significantly less bioavailable when consumed without a high-fat meal.

Prior to submission of the original NDA, the sponsor did not attend an end-of-phase two meeting and did not attend a preNDA meeting. During multiple meetings from 2002 to 2006 the sponsor was advised that if their product was not bioequivalent to the listed drug, clinical trials safety data would be required to establish efficacy. During a preIND meeting on 16July2001 the agency recommended the applicant complete a phase two dose ranging study and a phase three clinical study comparing the safety and efficacy of their product and the listed drug; upon receipt of the original IND on 7June 02 the

agency advised that it was highly unlikely that pharmacokinetic studies alone would support safety and efficacy for the CIP-Isotretinoin product; at a guidance meeting on 21May03 the agency again stated that if any of the dosage sizes were found to be more bioavailable than the same size capsule of Accutane®, then clinical trials would be necessary; and at a guidance meeting on 28 April 04 the agency reiterated that the pivotal in vivo bioequivalency trials are considered to be those under fasted conditions.

On May 1, 2006 the submission was determined to be “approvable” upon resolution of multiple clinical and chemistry deficiencies. The original application contained only pharmacokinetic studies and no clinical safety studies comparing the proposed drug product to the listed drug product. Based upon the lack of bioequivalence in the fasted state, the application did not establish an adequate basis for the agency to rely upon the previous findings of safety and effectiveness for the listed drug, Accutane®. The agency recommended that the sponsor conduct a clinical safety and efficacy trial or a population PK study comparing CIP-Isotretinoin to Accutane® at a dose of 1.0mg/kg/day.

Additional deficiencies included failure to demonstrate dose proportionality across the proposed dosage strengths, inadequate listing of the test materials facilities that will perform quality control, inadequate justification of the in-process controls for the proposed commercial scale batches, and the need for clarification of the analytical method for the dissolution test. The sponsor made a commitment to participate in a risk management program.

The sponsor did not request a meeting with the agency to discuss the deficiencies in the original submission of 27June05.

Clinical

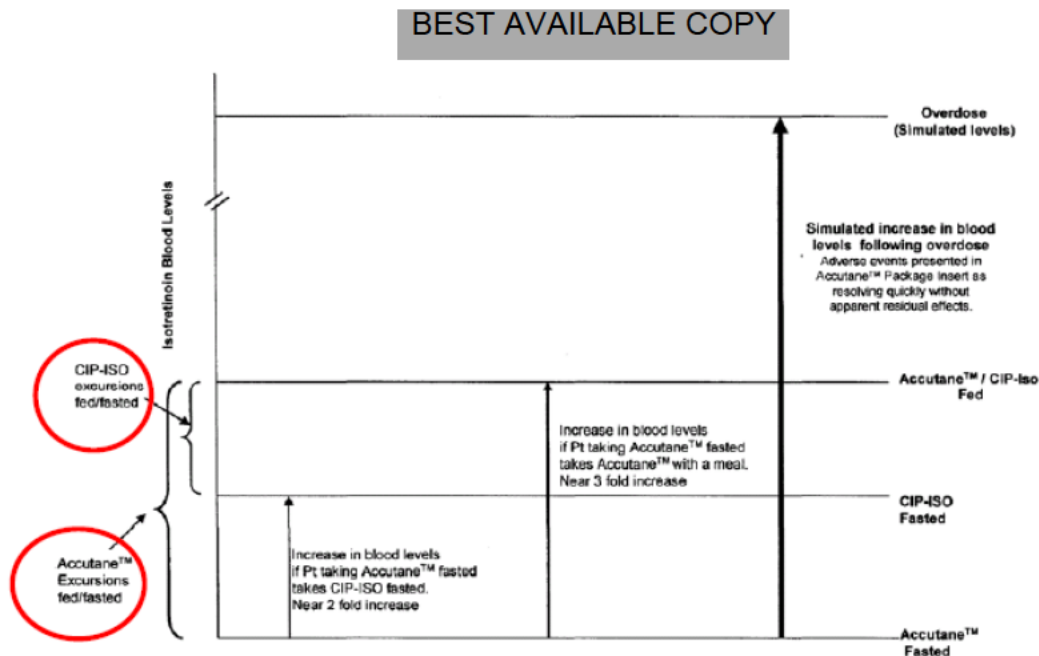
Deficiency 1: Safety and Efficacy

I concur with the medical and clinical pharmacology reviewer conclusions that the sponsor should conduct a clinical trial to demonstrate the safety of their drug product in comparison to the listed drug. The pharmacokinetic profile for the CIP-Isotretinoin product demonstrates that fasted levels of CIP-Isotretinoin are approximately 200% (2x) more bioavailable compared to the listed drug. Over the *course of therapy* all patients, fed or fasted, can be predicted to have increased exposure to isotretinoin from CIP-Isotretinoin than if they were prescribed the listed drug. It is absolutely unknown how this difference in exposure may affect the safety profile of the CIP-Isotretinoin product. Without head to head clinical trial data, there is insufficient information to establish a safety bridge to the listed product, Accutane®.

The requirement for demonstrating safety of the CIP-Isotretinoin product cannot be adequately fulfilled by comparing CIP-Isotretinoin bioavailability profile to the reference drug, as is proposed by the applicant. The applicant has conducted a multi-dose bioequivalence trial (2003-666) demonstrating that under fed conditions, the CIP-Isotretinoin product has a similar rate and extent of exposure as that of Accutane®,

although there was still a considerable amount of variability in the dataset. However, under fasted conditions (2003-627), the products are markedly different, in that the CIP-Isotretinoin product demonstrates greater bioavailability. This difference leads to significant concerns about the safety outcomes for patients during a course of treatment with the CIP-Isotretinoin product, because the CIP-Isotretinoin patients would likely have higher exposure to isotretinoin during the treatment period of 15-20 weeks. The safety concern that must be addressed by the applicant is to demonstrate the impact (or lack thereof) of this differential bioavailability on patient safety during this entire treatment period.

The sponsor has clearly demonstrated bio-inequivalence in the fasted state, so demonstrating bioequivalence for their current product is not a possibility. The sponsor's deficiency is that because their product is more bioavailable than the listed product, and the impact of this increased exposure to isotretinoin over the course of therapy has not been demonstrated. A 505(b) (2) "bridge" for safety cannot be demonstrated by the short-term pharmacokinetic data submitted to date.



The argument has been made that because the levels of isotretinoin in CIP-Isotretinoin fall "within" the range of known levels for Accutane®, the CIP-Isotretinoin product should have no additional burden of safety and should be approved. The problem with this argument is that it *assumes* that patients taking CIP-Isotretinoin and patients taking Accutane® will have similar safety profiles. This cannot be assumed. Patients taking CIP-Isotretinoin will occupy exposures in the upper band of patients taking Accutane®. Given that real world use of Accutane® likely includes exposures under fasted conditions, it is reasonable to assume that Accutane® users experience a range of

exposures that are lower than anticipated for the Cipher product, and that these lower exposure could mitigate against dose-related toxicities. The effect of the actual circulating level of isotretinoin (high or low) upon the *incidence* of adverse events, the *type* of adverse events, or the *severity* of adverse events is unknown. It is reasonable to be concerned that when patients begin taking an isotretinoin formulation that is relatively food independent, the exposure to isotretinoin will be increased during the course of treatment. The impact on adverse events is unknown. It is this uncertainty that demands a clinical trial to establish the safety profile of CIP-Isotretinoin. This information can only be derived from a clinical study powered for safety.

The listed product is labeled to be taken with meals, and the CIP-Isotretinoin product proposes similar labeling. An argument has been made that as both products are labeled to be taken with food, the agency should only use data from patients in the “fed” state to reach a conclusion on this application. The applicant has provided data establishing that the CIP-Isotretinoin product has a real and significant potential for increased bioavailability during the treatment course. Teenagers and young adults are more likely to eat a sparse breakfast, if indeed they eat breakfast at all. Approval of the enhanced bioavailability CIP-Isotretinoin product by allowing a safety “bridge” to the Accutane® safety data would potentially place patients taking the CIP-Isotretinoin product at an extraordinary risk. Our understanding of the safety profile of Accutane® is based upon the original clinical trials and more than two decades of post-marketing safety data. Significant safety information related to isotretinoin has emerged during the post-marketing period, including concerns about systemic toxicities and potential neuro-psychiatric events. Investigations are essential to demonstrate the safety of the CIP-Isotretinoin product.

Study 627 Fasted Treatments (n=57) Arithmetic Means			
	Cipher 2x20mg	Accutane(tm) 40mg	T/R*100
AUC _t (ng*hr/ml)	4307 (29%)	2349 (29%)	183%
AUC _{inf} (ng*hr/ml)	4676 (28%)	2619 (30%)	179%
C _{max} (ng/mL)	347 (35%)	169 (29%)	205%
Study 627 Fed Treatments**			
AUC ₂₄ (ng*hr/ml)	6400 (20%)	6145 (26%)	104%
AUC _{inf} (ng*hr/ml)	6858 (21%)	6561 (26%)	104%
C _{max} (ng/mL)	466 (38%)	471 (41%)	98.9%

For demonstration of efficacy, it would be reasonable to conclude that patients treated with the CIP-Isotretinoin product will consistently have isotretinoin levels in the higher ranges of those demonstrated for Accutane® patients. For this 505 (b)(2) application, it would be difficult to propose a reasonable argument describing why the bioavailability of CIP-Isotretinoin at levels similar to the highest levels of bioavailability of the listed drug would NOT be adequate to establish efficacy.

Conclusion: The clinical deficiency has not been resolved. Clinical investigations are essential to demonstrate the safety of the CIP-Isotretinoin product. Clinical trial design and conduct should be agreed upon between the agency and applicant prior to initiation of studies.

Deficiency 2: Risk Management Program

The sponsor has agreed to participate in a risk management program. Cipher's product would be dispensed in accordance with the iPledge risk management program and discussions between the agency and sponsor will continue in future submissions. As the sponsor has agreed to participate in a risk management program, specifics will be resolved during a future approval cycle.

Deficiency 3: Dose proportionality

The sponsor has addressed the issue of dose proportionality across the individual dosage strengths of their own product through two head to head studies (1 fasted and 1 fed) and two biopharmaceutic expert reports. The studies compared the Cipher 30mg product to 3 x 10mg Cipher product in approximately 50 subjects each. The sponsor demonstrated adequate dose proportionality both between the two treatments (30 mg vs. 10mg x3) and between the fed and fasted states. Study PK 06.02 also demonstrates a variable food effect for the Cipher product, with AUC (1.7x) and CMax (1.5x) increased in the fed vs. fasted state.

The sum of this information and information provided in the original submission adequately addresses the dose-proportionality deficiency.

Chemistry, Manufacturing, Controls

Deficiency 4, 5, 6, 7

4. List the testing materials facilities that will perform quality control (Manufacture)
Sponsor has satisfied this deficiency as described in CMC review section III (1)
5. Justify the in-process controls for the proposed commercial scale batches (Control).
Sponsor has satisfied the deficiency as described in CMC review section III (2)
6. Establish multiple time points based on dissolution profiles (Specifications)
Sponsor has not satisfied this deficiency as described in CMC review Section III (3). CMC comments were forwarded to the sponsor on Feb 12, 2007 and a response has not been received. The issue to be resolved is whether or not the drug product can be labeled as an "immediate release" formulation. As the application will not be approved during this cycle, resolution of this dissolution issue can be expected during a future cycle.
7. Analytical method for dissolution test requires clarification (Validation)

The sponsor has satisfied this deficiency as described in CMC review section III (4)

REGULATORY CONCLUSION:

NDA 21-951 remains “approvable”, pending resolution of the following deficiencies:

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®.
2. The proposed dosage form is considered to be an (b) (4) capsule. The dissolution test should be established with multiple time points.

Susan J. Walker, M.D.
Division Director
Dermatology and Dental Products
OND/ODEIII/CDER

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Susan Walker
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DIRECTOR

NDA 21-951 AZ Response to AE
Dermatology Clinical Team Leader Summary Memorandum

April 19, 2007

Drug: Cip-Isotretinoin (isotretinoin) Capsules 10, 20 and 30 mg.

Manufacturer: Cipher Pharmaceuticals

Indication Sought: Severe recalcitrant nodular acne

Background

Isotretinoin is currently marketed as Accutane 10, 20, and 40 mg Capsules and in the form of various branded generics. Cipher Pharmaceuticals submitted an NDA on July 1, 2005, for a new formulation of isotretinoin via 505(b)(2) with a claim that this formulation is more bioavailable when administered fasted than Accutane. Generic versions of isotretinoin are required to be bioequivalent in both the fasted and fed states for approval. An approvable letter reaffirming the discussions held with the sponsor prior to NDA filing that clinical studies would be required for approval was sent on May 1, 2006. The items cited in this letter included, but were not limited to, a clinical and /or population PK study to further evaluate safety concerns potentially associated with the increased isotretinoin exposure from Cip-Isotretinoin under fasted condition when compared to Accutane.

Summary of Review Issues

Clinical - The current submission from Cipher, dated October 27, 2007, is a response to the Approvable (AE) letter. In this submission, no new clinical data was submitted to address the deficiencies highlighted in the AE letter beyond that from two single dose dose-proportionality studies addressing item #3 in the letter. Rather, the sponsor reaffirms the potential for greater bioavailability from an equal milligram dose of their formulation of isotretinoin under fed conditions.

Dr. Denise Cook, the FDA primary clinical reviewer, in her review for the original submission had safety concerns regarding the higher fasted bioavailability of Cip-Isotretinoin. Specific concerns included a higher number of psychiatric adverse events seen in the Cip-Isotretinoin treatment arm as compared to Accutane in a small multiple dose PK study and potential for lipid profile changes. These concerns have not been mitigated in any manner in the current submission, a response to the previous negative action for this NDA.

Biopharmaceutics - The Clinical Pharmacology and Biopharmaceutics Review by Dr. Dennis Bashaw encompasses the dose proportionality information submitted by the sponsor. Information was needed to address this issue and was requested in the May 1, 2006 action letter. Dr. Bashaw indicates that the current submission adequately addresses the issue of dose proportionality, however, the review also indicates concern regarding the safety and efficacy database needed for this application. Specifically the concern that

occupancy of this product at the high end of the expected range of exposures from Accutane over a 20 week course of therapy would result in a different safety profile for Cip-Isotretinoin, requiring a separate safety determination.

Chemistry – Dr. Tarun Mehta reviewed the most recent submission with regard to responses to noted deficiencies for the proposed product. A single issue remains with regard to the immediate release dissolution specification for this product needing to have multiple time points with acceptance criteria for each time point.

Regulatory Recommendation

The Dermatology Clinical Team Leader recommends that clinical information regarding comparative safety to Accutane is needed before approval for this new formulation of isotretinoin. This recommendation is consistent with the previous recommendation from the last review cycle for this NDA. For a 505(b)(2) application, the sponsor has failed to establish an adequate bridge to the Accutane formulation of isotretinoin to allow for approval.

Cip-Isotretinoin is not bioequivalent to Accutane under fasted conditions, having demonstrated increased fasted bioavailability in the comparative pharmacokinetic study which was carried out under controlled dietary conditions. Use of this product in a “real world” setting would potentially lead to a greater bioavailability vis a vis Accutane and result in potentially a different safety and profile related to the improved bioavailability performance in the fasted state. It is strongly recommended that this difference be explored more carefully in clinical studies prior to approval. This concern was conveyed in the action letter dated May 1, 2006. The sponsor has not taken adequate steps to remedy this lack of information in the most recent submission.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke

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MEDICAL OFFICER

Team Leader Summary Memorandum on Cipher Cip-Isotretinoin.

Susan Walker

4/19/2007 11:33:46 PM

DIRECTOR

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-951
Submission Code	000 AZ

Letter Date	10/26/06
Stamp Date	10/27/06
PDUFA Goal Date	4/27/07

Reviewer Name	Denise Cook, M.D.
Review Completion Date	4/10/07

Established Name	Isotretinoin
(Proposed) Trade Name	Cip-Isotretinoin
Therapeutic Class	Oral Retinoid
Applicant	Cipher Pharmaceuticals, LTD

Priority Designation	S
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Formulation	Oral
Dosing Regimen	0.5 mg/kg/day – 2.0 mg/kg/day
Indication	Severe Recalcitrant Nodular Acne
Intended Population	Ages 12 – Adult

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that from a clinical perspective, NDA 21-951, for oral isotretinoin (Cip-Isotretinoin) capsules, 10 mg, 20, mg, and 30 mg, for the treatment of severe, recalcitrant nodular acne should receive a “non-approvable” action. The original application was submitted as a 505(b)(2) with Accutane as the reference listed drug (RLD). This application was submitted as a “complete” response by the sponsor to an approvable action letter issued by the division on May 1, 2006. However, this application only addressed one deficiency outlined in the action letter, namely, dose proportionality across its different dosage forms. While this was adequately demonstrated, according to the review by Dr. Dennis Bashaw, the application does not address the pivotal reason that marketability was denied, namely, the establishment of an adequate bridge to Accutane such that the Agency could rely on the previous findings of safety and effectiveness for this RLD.

The original NDA did not contain any clinical trials. The sponsor attempted to establish safety and efficacy via pharmacokinetic studies, both single and multidose. Non-approval for the original NDA was recommended for the following reasons:

1. The different PK profile of Cip-Isotretinoin does not allow for extrapolation of primarily the safety profile of Accutane and does not guarantee efficacy, either. Since Accutane has a myriad of serious adverse events that can occur during treatment, this difference in PK profile, in the absence of a clinical trial, makes the risk/benefit analysis for this product unacceptable for marketing, as it is essentially unknown.

2. While meaningful safety conclusions cannot be ascertained from the small safety data base of an 11 day pk study, the signal from the small safety data base obtained from one of the multi-dose PK studies underscores the need for further study of this drug product.

The “action” letter addressed the primary deficiency for which the NDA was not approved for marketing. Namely the following:

“The application did not establish, by way of bioavailability data comparing CIP-Isotretinoin to Accutane®, an adequate basis for the Agency to rely on the previous finding of safety and effectiveness for the referenced listed drug, Accutane, to approve CIP-Isotretinoin. In addition, 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 and efficacy of CIP-Isotretinoin. Your claim of no difference in terms of safety and effectiveness between CIP-Isotretinoin and the listed drug cannot be supported without clinical trial data.

To address this deficiency, we recommend that you conduct a clinical safety and efficacy 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% of the population for safety. The following additional items are important for adequate labeling and should be addressed in the same study:

- *Prospective assessment for psychiatric and CNS events by specialists and appropriate instruments, with attention to risk factors and response to intervention*
- *Adequate monitoring for bone mineral density changes and premature closure of the epiphyses*
- *Adequate testing for hearing and vision impairment with sufficient follow-up to inform labeling regarding reversibility*
- *Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility*

As an alternative to the clinical trial described above, you could conduct a comparative population pk study in a suitably large number of subjects (>200 per arm) with severe recalcitrant nodular acne. The study would use pre-defined measures of comparability to demonstrate that the plasma levels for the test and reference product are similar under real world conditions for a suitable duration (dosed for a clinical course of 20 weeks). The actual design elements would have to be agreed upon with the Agency and the Pharmacometrics group within the Office of Clinical Pharmacology prior to initiation. Depending on the results of this trial, a second trial with clinical safety and efficacy endpoints maybe necessary if the variability seen in the data is deemed sufficient to raise concern.” (The reader is referred to Appendix 1 for the entire contents of the approvable letter).

The sponsor did not conduct either the clinical trial that was requested or the population pharmacokinetic study in this resubmission. Thus, the resubmission, with only dose proportionality studies, is not adequate for this NDA to be approved via a 505(b)(2) route with Accutane as the RLD.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

As stated before, there were no clinical studies conducted under this resubmission of NDA 21-951. Thus, there is no efficacy data and the small amount of safety data is generated only from the dose proportionality studies, in which patients received a single dose of Cip-Isotretinoin. The dose studied was a single dose of 3x10 mg Cip-Isotretinoin under fed and fasted states compared to one 30 mg capsule of Cip-Isotretinoin under fed and fasted conditions.

1.2.2 Efficacy

The quotes below from the sponsor provides their argument for the efficacy of Cip-Isotretinoin as compared to Accutane in the absence of clinical trial data.

“That CIP-ISOTRETINOIN is not bioequivalent to AccutaneTM when administered fasted is irrelevant in considering CIP-ISOTRETINOIN’s efficacy. The whole point of CIP-ISOTRETINOIN is to be more bioavailable than AccutaneTM when administered fasted, and it is.”

The sponsor then surmises the following:

“From an efficacy standpoint, a drug for which the blood levels more closely approximate fed levels when administered fasted, must be at least as effective (if not more so) than the approved

drug, because there is less fasting-related loss of drug in the blood stream. In addition, the Division should consider that the higher fasted blood levels resulting from CIP-ISOTRETINOIN compared to AccutaneTM may in fact provide a safety benefit, by preventing the need for retreatment with a second course of isotretinoin.”

In this reviewer’s opinion, the exact nature of the efficacy of Cip-Isotretinoin is not known. Certainly, one might surmise that since higher levels of Cip-Isotretinoin are achieved under fasted conditions, and subjects are not likely to take the medication with a high fat meal for 20 weeks, that the efficacy might be better. However, this is not certain, for higher blood levels do not always translate into higher efficacy but usually translates into higher toxicity. Given that Accutane cures 80% of subjects who are treated for severe, recalcitrant nodular acne, any additional efficacy would have to be weighed very carefully against additional toxicity. The absence of a clinical trial against Accutane (the RLD) in this application makes this analysis impossible.

1.2.3 Safety

Patients taking one 30 mg dose of Cip-Isotretinoin experienced adverse events that are known to occur with isotretinoin, including headache and lipid and liver alterations. There was one event of disorientation that lasted for 26 hours post dosing. Most adverse events resolved except hypercholesterolemia. As these events occurred after a single dose and in such a small population, no meaningful conclusions regarding the safety of Cip-Isotretinoin for the intended use of the drug, which is for 15-20 weeks at a range of 0.5 mg/kg/day- 2.0 mg/kg/day, can be made.

1.2.4 Dosing Regimen and Administration

There is no change from the request in the original NDA for the dosing and administration of Cip-Isotretinoin. Namely, the sponsor is requesting the same dosing and administration as that of Accutane. That is, that is the drug should be given in a dose from “0.5 mg/kg/day to 1.0 mg/kg/day in two divided doses with food for 15 – 20 weeks.” Accutane can be given, for more severe cases, up to 2.0 mg/kg/day.

1.2.5 Drug-Drug Interactions

No drug-drug interactions were studied in this NDA.

1.2.6 Special Populations

There is no change from the original NDA submission. The applicant asked for a waiver for the pediatric population. A waiver can be granted for patients less than 12 years of age, as severe, nodular acne does not occur in this age group. Patients 12 years and older will need to be incorporated into any clinical trial conducted to seek approval for Cip-Isotretinoin.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.11 Description of the Product

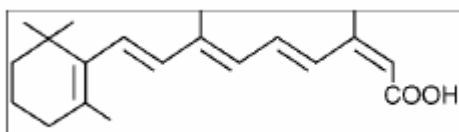
Isotretinoin, a retinoid, is available as CIP-ISOTRETINOIN in 10 mg, 20 mg and 30 mg gelatin capsules for oral administration. Each capsule contains isotretinoin, stearyl macrogol glycerides, soybean oil, sorbitan monooleate, propyl gallate, gelatin, titanium dioxide and iron oxide.

2.12 Established Name and Proposed Trade Name

The established name of the drug product is isotretinoin. The proposed trade name is Cip-Isotretinoin. The product will be referred to as Cip-Isotretinoin throughout this review.

2.13 Chemical Class

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



2.14 Pharmacological Class

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

2.15 Proposed Indication, Dosing Regimen, Age Groups

Indication

CIP-ISOTRETINOIN is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become supportive or hemorrhagic. "Severe," by definition², means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, CIP-ISOTRETINOIN should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, CIP-ISOTRETINOIN is indicated only for those

females who are not pregnant, because CIP-ISOTRETINOIN can cause severe birth defects (see boxed CONTRAINDICATIONS AND WARNINGS).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.^{1,3,4} If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off CIP-ISOTRETINOIN. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (b) (4)

(b) (4)

Reviewer's Comment: *This entire section is predicated on Cip-Isotretinoin's ability, through a 505(b)(2) route, to borrow the FDA's findings of safety of Accutane, the reference listed drug product. The sponsor did not perform any clinical studies to ascertain the safety of Cip-Isotretinoin, which is not bioequivalent to Accutane. It should be noted that the sponsor wants the same label as Accutane except for the biopharm section of the label.*

2.2 Currently Available Treatment for Indications

The best currently available treatment for severe, recalcitrant nodular acne is Accutane and its generics, three which are currently marketed, Amnesteem, Claravis, and Sotret. The generic products were required to be bioequivalent to Accutane in both the fed and fasted state.

Accutane and its generics cure the disease in 80% of patients after one 20-week course of treatment with doses that range from 0.5 mg/kg/day – 1.0 mg/kg/day. Rarely are higher doses needed, but the products are approved for up to 2mg/kg/day. Less than 20% of patients who fail need a second course of treatment. Some of these patients may exhibit a milder form of acne which is amenable to topical treatment and/or possibly systemic antibiotics.

2.3 Availability of Proposed Active Ingredient in the United States

Isotretinoin is readily available in the United States.

2.4 Important Issues With Pharmacologically Related Products

Isotretinoin, as a class of products, is approved under Subpart H in the United States because it is a potent human teratogen. It also causes a myriad of serious side effects. Neurological/psychiatric adverse events include mood alteration, violent behavior, depression, and suicide. Central nervous system effects include pseudotumor cerebri, CNS developmental abnormalities, and headaches. Other organ systems that can be affected include lipid alterations with elevations of serum triglycerides which has led to acute pancreatitis in some cases, and to a lesser extent elevations in serum cholesterol; increases in liver function tests, including hepatitis; hearing impairment; vision impairment; musculoskeletal effects which have included decreases in bone mineral density, delayed healing of bone fractures, and premature epiphyseal closure; and inflammatory bowel disease in patients without a pre-existing history.

2.5 Presubmission Regulatory Activity

- PreIND Meeting – July 16, 2001
 - Sponsor proposed to conduct PK studies and a single phase 2/3 clinical trial to support a 505(b)(2) application
 - Advice from Agency
 - phase 2 dose ranging study

- phase 3 trial comparing Cip-isotretinoin either bid or q day or both to Accutane bid
- Original IND (b) (4) – June 7, 2002
 - The sponsor was advised, “The clinical benefit of increased bioavailability is unclear unless it involves food independence.”
 - “It is highly unlikely that PK studies will support the safety and efficacy of dosing equivalent to Accutane.”
 - “We strongly support clinical testing of once daily dosing vs. BID dosing.”
 - “If a comparable dose of Accutane (based on data from your PK studies) was included in a third arm, this one well-powered trial, combined with data from the P2 study, *might* allow comparative safety and efficacy labeling.”
- Guidance Meeting – May 21, 2003
 - Sponsor was advised to explain lack of dose proportionality for their drug product
 - Advised, “If any of the dosage sizes are found to be more bioavailable than the same size capsule of Accutane, (for example, 10 mg) then clinical trials will be necessary.”
- Guidance Meeting – April 28, 2004
 - Sponsor was advised, “From a bioequivalence standpoint, the pivotal in vivo bioequivalency trials are considered to be those under fasted conditions.”
 - “Any considerations that could be perceived as an advantage with the Cipher product should be demonstrated and proven clinically.”
- Original NDA 21-951 – Submitted on 6/27/05 with a stamp date of 7/1/05
 - Regulatory briefing held on March 26, 2006 – it was concluded from this meeting that more information was needed before approval.
 - May 1, 2006 – an approvable action letter was issued which is attached to this review as appendix 1.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The action letter on May 1, 2006 outlines several chemistry deficiencies, none of which were addressed in this submission.

3.2 Animal Pharmacology/Toxicology

The submission is a 505(b)(2), thus the sponsor is relying on the safety findings from Accutane, the RLD. No new pharm/tox data was submitted with the original or this resubmission.

4 CLINICAL PHARMACOLOGY

The sponsor submitted two dose proportionality studies in this NDA which were reviewed by Dr. E. Dennis Bashaw. Dose proportionality was demonstrated through 2 head-to-head studies of their own product in both the fed and fasted state using two treatments – 3x10 mg and 1x30 mg.

Study ISO PK.06.01 was a single dose study comparing 3 x 10 mg Cip-Isotretinoin to 1 x 30 mg Cip-Isotretinoin in the fasted state. Fifty (50) subjects completed the study. The second study, ISO PK.06.02, was a single dose study comparing 3 x 10 mg Cip-Isotretinoin to 1 x 30 mg Cip-Isotretinoin in the fed state. Fifty-two (52) subjects completed this study. Both were randomized trials with a 3-week washout period between treatment arms.

Dr. Bashaw found that for study 06.01, although the 90% confidence intervals do not pass for AUC, they are just outside the acceptance interval for dose proportionality. In study 06.02, he found that all of the 90% confidence intervals do pass for AUC (tau and inf) and Cmax. He also found that Cip-Isotretinoin demonstrates a significant food effect, with ACUinf increased roughly 1.7x and Cmax by 1.5x.

Dr. Bashaw's conclusion was that dose-proportionality was demonstrated and that the sponsor had satisfied item #3 of the action letter (the reader is referred to the biopharmaceutics review for complete details).

5 INTEGRATED REVIEW OF EFFICACY

The quotes below from the sponsor provide their argument for the efficacy of Cip-Isotretinoin as compared to Accutane in the absence of clinical trial data.

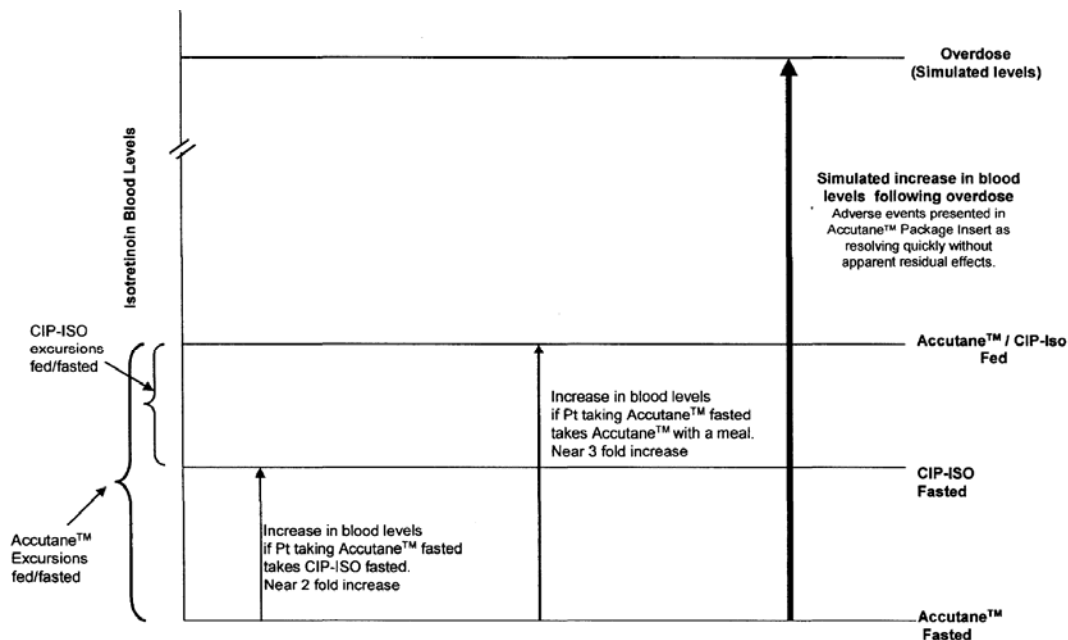
“That CIP-ISOTRETINOIN is not bioequivalent to AccutaneTM when administered fasted is irrelevant in considering CIP-ISOTRETINOIN's efficacy. The whole point of CIP-ISOTRETINOIN is to be more bioavailable than AccutaneTM when administered fasted, and it is.”

The sponsor then surmises the following:

“From an efficacy standpoint, a drug for which the blood levels more closely approximate fed levels when administered fasted, must be at least as effective (if not more so) than the approved drug, because there is less fasting-related loss of drug in the blood stream. In addition, the Division should consider that the higher fasted blood levels resulting from CIP-ISOTRETINOIN compared to AccutaneTM may in fact provide a safety benefit, by preventing the need for retreatment with a second course of isotretinoin.”

In the submission dated April 18, 2006, the sponsor provided the following graph in Figure 1 to illustrate their position (taken from biopharm review, page 10):

Figure 1



This graph actually describes our concern. The sponsor interprets the increased bioavailability as a possible increase in efficacy, which in turn will improve the safety profile because of a purported decrease in the need for retreatment. In this reviewer's opinion, the increased bioavailability of Cip-Isotretinoin in the fasted state as compared to Accutane may not, as the sponsor proposes, translate into greater efficacy, but may translate into greater safety concerns during a single 20-week course of treatment, without necessarily any added efficacy benefit. The only way to ascertain the benefit/risk calculus for this drug, as it is not bioequivalent to Accutane, is through a clinical trial.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Finding

The overall safety data base for this submission is from the 2 single-dose, dose proportionality trials.

6.1.1 Deaths

There were no deaths in the two trials.

6.1.2 Dropouts and Other Significant Adverse Events

In study 06.01, there were 4 discontinuations. Subjects 28 and 38 voluntarily withdrew for personal reasons after the completion of period 1, subject 29 withdrew due to abdominal pain prior to period 2, which according to the CRF was secondary to a parasitic infection, and subject 42 was dismissed after testing positive for cotinine. There were not any discontinuations in study 06.02.

6.1.2.1 Other significant adverse events

In study 06.02, one patient, patient 41, had an adverse event of disorientation. The patient was dosed with medication on 6/20/06 at 0841, disorientation was noted on 6/21/06 at 0440 and resolved on 6/22 at 0600. There was no other characterization of the disorientation except to note that it was mild. This reviewer is assuming this is the patient that the sponsor listed as having confusion, as there was no other patient with a similar adverse event in this study, according to the CRFs.

6.1.3 Common Adverse Events

In study 06.01, there were 63 adverse events broken down as follows:

Treatment A – (3 x 10 mg)

There were 30 AEs associated with this arm, which consisted of:

- HYPERCHOLESTEREMIA (4)
- HEADACHE (3)

- HYPERLIPEMIA (2)
- CREATININE INCREASE (2)
- DIZZINESS (2)
- TACHYCARDIA (2)
- SWEAT (2)
- PALLOR (2)
- DRY MOUTH (2)
- SGOT INCREASE (2)
- THROMBOCYTOPENIA (1)
- BRADYCARDIA (1)
- NAUSEA (1)
- HYPERGLYCEMIA (1)
- VASODILATION (1)
- HYPERTENSION (1)
- HYPOCHOLESTEREMIA (1)

Treatment B (1 x 30 mg)

There were 33 AEs associated with this arm and consisted of:

- SGPT INCREASE (4)
- TACHYCARDIA (3)
- HYPERCHOLESTEREMIA (3)
- SGOT INCREASE (3)
- HEADACHE (3)
- URINARY ABNORMALITY (3)
- LDH INCREASE (2)
- ECCHYMOSIS (2)
- RASH (1)
- DIZZINESS (1)
- HYPERTENSION (1)
- GGTP INCREASE (1)
- PAIN ABDOMEN (1)
- BUN INCREASE (1)
- CREATININE INCREASE (1)
- NAUSEA (1)
- DIARRHEA (1)
- HYPERLIPEMIA (1)

In study 06.02, there were 48 adverse events.

Treatment A (3 x 10 mg)

There were 22 AEs associated with this arm of the study and consisted of:

- PRURITUS (6)
- HEADACHE (2)
- HYPERTENSION (2)
- HYPERGLYCEM (2)
- DIZZINESS (1)
- HYPOTENS (1)
- DRY MOUTH (1)
- RHINITIS (1)
- ECCHYMOSIS (1)
- STOMATITIS (1)
- ACNE (1)
- THIRST (1)
- HYPERCHOLESTEREM (1)
- HYPERLIPEMIA (1)

Treatment B (1 x 30 mg)

There were 26 AEs associated with this arm, which consisted of:

- HYPERTENSION (5)
- LEUKOCYTOSIS (3)
- THROMBOCYTOPENIA (2)
- HEADACHE (2)
- URINARY ABNORMALITY (2)
- RHINITIS (2)
- SOMNOLENCE (2)
- PAIN ABDOMEN (1)
- RASH (1)
- CREATININE INCREASE (1)
- NAUSEA (1)
- EDEMA FACE (1)
- DIARRHEA (1)
- PRURITUS (1)
- CONFUSION(1)

6.1.3.1 Eliciting adverse events data in the development program

Subjects were questioned throughout the study regarding their health status.

6.2 Adequacy of Patient Exposure and Safety Assessments

One cannot make meaningful safety conclusions from the safety data base of single dose studies. This drug product is proposed to be used over a course of treatment that may last from 15 – 20 weeks. Therefore, to ascertain safety, a clinical trial of that duration is necessary.

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

6.2.1.1 Study type and design/patient enumeration

Both studies were single-dose studies with a 3 week washout period between the fed and fasted arms. In study 06.01, the safety population totaled 54 for period one which began on June 16, 2006 and 50 subjects completed period 2 which began on July 7, 2006. For study 06.02, 52 subjects completed both period 1 and period 2.

6.2.1.2 Demographics

In study 06.01, demographic data was provided for the 50 subjects who completed the entire study. The mean, standard deviation and range of the data is as follows:

- Age: 37 ± 9 yrs (21 — 54 yrs)
- Height: 170.3 ± 7.8 cm (155.5 — 187.0 cm)
- Weight: 75.2 ± 9.4 kg (56.1 — 90.8 kg)
- BM1: 25.9 ± 2.3 (19.7 — 29.9)

In study 06.02, demographic data was provided for the 52 subjects who completed the study. The mean, standard deviation and range of the data is as follows:

- Age: 37 ± 9 yrs (21 — 54 yrs)
- Height: 170.3 ± 7.8 cm (155.5 — 187.0 cm)
- Weight: 75.2 ± 9.4 kg (56.1 — 90.8 kg)
- BM1: 25.9 ± 2.3 (19.7 — 29.9)

6.2.1.3 Extent of exposure (dose/duration)

These were single dose studies, with a 3 week washout period between arms.

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

One cannot make any meaningful conclusions regarding the safety of Cip-Isotretinoin over a 15-20 week course of treatment from a single dose study.

7 OVERALL ASSESSMENT

7.1 Conclusions

It can be concluded from this resubmission of NDA 21-951 that the sponsor has satisfied item 3 (see appendix 1) of the action letter; that is, that there is dose proportionality among the different dosages of Cip-Isotretinoin. However, these dose proportionality studies do not address the main substance of the action letter, which is the fact that as Cip-Isotretinoin is not bioequivalent to Accutane, and given the safety profile of Accutane, the Agency still cannot rely on the previous finding of safety and effectiveness for the referenced listed drug, Accutane, to approve Cip-Isotretinoin.

As stated in my conclusion of the original submission, pharmacokinetic data revealed that Cip-Isotretinoin is not bioequivalent to Accutane. In the fasted state, Cip-Isotretinoin is much more bioavailable than Accutane. This is of importance because in the real world, it is unlikely that a high fat diet, such as the one used in the studies, will be consumed by the patient twice a day for 15-20 weeks (the course of treatment). Teenagers and young adults are more likely to eat a sparse breakfast, if indeed, they eat breakfast at all. Evening meals may also vary in consistency from low-fat to high fat. Thus, patients taking Cip-Isotretinoin, most likely will be exposed to consistently higher levels of isotretinoin, and potentially more serious adverse events.

In conclusion, Cip-Isotretinoin has not established an adequate biobridge of safety through pk studies to the reference listed drug product, Accutane. In essence, it has a different PK profile compared to Accutane. Thus, the safety and efficacy of this drug product compared to Accutane is unknown. Given the serious nature of adverse events that can occur in patients who take Accutane, such as depression, suicide, decreased bone mineral density, altered lipid homeostasis, hepatitis, and teratogenicity, it is important to ascertain what effects an increased bioavailable form of isotretinoin would have on the safety and efficacy profile in the indicated population. This is particularly true for neuropsychiatric events where the pathogenesis is unclear. That is, it is not known if the events are related to increased AUC and Cmax values or to higher steady state exposures. The sponsor was advised from the beginning of their drug development for Cip-Isotretinoin that any bioinequivalence to Accutane would necessitate clinical trials. The efficacy and safety of this drug product as it compares with Accutane is unknown.

7.2 Recommendation on Regulatory Action

As the sponsor did not address the major outstanding issue of the action letter of May 1, 2006, that is, the conduct of a clinical trial, comparing Cip-Isotretinoin to the RLD, Accutane, at 1.0mg/kg/day in the intended population to establish an adequate biobridge for safety and efficacy, this application should receive a non-approval, as was recommended in the original NDA submission.

The applicant should conduct a clinical trial with a sufficient number of patients to detect an incidence of an adverse event occurring in 1% of the population for safety. This trial should be a head-to-head trial with Accutane. Efficacy should be ascertained in this trial, also, as Cip-Isotretinoin should be non-inferior to Accutane.

7.3 Comments to Applicant

As outlined in the action letter of May 1, 2006, the sponsor should conduct the following:

1. A phase 3 safety and efficacy trial in patients with severe, recalcitrant nodular acne where Cip-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day. This trial should have a sufficient number of patients, in all age groups in which the disease occurs, to detect an incidence of an adverse event occurring in 1% of the population for safety.

The following additional items, at a minimum, important for adequate labeling, should be addressed in the same study:

- Prospective detailed delineation of psychiatric and CNS events by specialists, with attention to risk factors and response to intervention
- Adequate monitoring for bone mineral density changes and premature closure of the epiphyses
- Adequate testing for hearing and vision impairment and follow-up to inform labeling regarding reversibility
- Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility

8 APPENDIX

8.1 Action Letter – May 1, 2006

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Arthur Deboeck, Vice President and General Manager
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Deboeck:

Please refer to your new drug application (NDA) dated June 27, 2005, received July 1, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10, 20, and 30 mg.

We acknowledge receipt of your submissions dated November 2, 3, and 17, and December 23, 2005 (2), and February 1 and 9, 2006. We also acknowledge receipt of your submission dated April 18, 2006. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application proposes the use of CIP-Isotretinoin 10, 20, and 30 mg Capsules for the treatment of severe recalcitrant nodular acne.

We have completed our review of this application, as amended, and it is approvable once the deficiencies outlined below are resolved.

Clinical

1. The application did not establish, by way of bioavailability data comparing CIP-Isotretinoin to Accutane®, an adequate basis for the Agency to rely on the previous finding of safety and effectiveness for the referenced listed drug, Accutane, to approve CIP-Isotretinoin. In addition, 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 and efficacy of CIP-Isotretinoin. Your claim of no difference in terms of safety and effectiveness between CIP-Isotretinoin and the listed drug cannot be supported without clinical trial data.

To address this deficiency, we recommend that you conduct a clinical safety and efficacy 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% of the population for safety. The following additional items are important for adequate labeling and should be addressed in the same study:

- Prospective assessment for psychiatric and CNS events by specialists and appropriate instruments, with attention to risk factors and response to intervention
- Adequate monitoring for bone mineral density changes and premature closure of the epiphyses
- Adequate testing for hearing and vision impairment with sufficient follow-up to inform labeling regarding reversibility
- Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility

As an alternative to the clinical trial described above, you could conduct a comparative population pk study in a suitably large number of subjects (>200 per arm) with severe recalcitrant nodular acne. The study would use pre-defined measures of comparability to demonstrate that the plasma levels for the test and reference product are similar under real world conditions for a suitable duration (dosed for a clinical course of 20 weeks). The actual design elements would have to be agreed upon with the Agency and the Pharmacometrics group within the Office of Clinical Pharmacology prior to initiation. Depending on the results of this trial, a second trial with clinical safety and efficacy endpoints maybe necessary if the variability seen in the data is deemed sufficient to raise concern.

2. We acknowledge your commitment to inclusion in a risk management program, such as iPLEDGE, for prevention of fetal exposure to isotretinoin.
3. The NDA does not have an adequate demonstration of proportionality across the proposed dosage strengths. As isotretinoin is dosed on a mg/kg basis and as it is expected that multiple dosage units will be used to obtain doses in the 0.5-1mg/kg range, then the relationship between the different strength capsules will need to be determined for CIP-Isotretinoin.

Chemistry, Manufacturing and Controls

4. Refer to NDA section 3.2.P.3.1 titled "Manufacture": List the testing facilities that will perform quality control test on bulk drug substance, components, intermediates, container/closure system and stability samples of finished drug product.
5. Refer to NDA section 3.2.P.3.4 titled "Control of Critical Steps and Parameters": Justify the in-process controls for the proposed commercial scale batches as the process

parameters used in the manufacture of clinical batches differ from the proposed commercial scale process parameters. See the comparison table below.



6. Refer to NDA section 3.2.P.5.1 titled "Specification": Establish multiple time points (30, 60, 120, and 240 minutes) based on typical dissolution profiles for the final (b) (4) dissolution test and for setting the acceptance criterion for each time point.
7. Refer to NDA section 3.2.P.5.3 titled "Validation of Analytical Procedure": The analytical method for the dissolution test is not the same as what had been used for the assay determination. If it is to be different, establish the LOQ, LOD for this specific method. In addition, establish the stability (shelf life) of the dissolution samples at room temperature stored in the HPLC vials.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Dermatology and Dental Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Melinda Harris-Bauerlien, M.S., Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Director
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Denise Cook
4/16/2007 09:44:58 AM
MEDICAL OFFICER

Markham Luke
4/16/2007 12:56:58 PM
MEDICAL OFFICER

Concur with recommendation not to approve based on the
information provided. Agree with need for additional clinical
studies to demonstrate safety and efficacy of the
proposed isotretiinoin product that has greater fasted bioavailability.

Susan Walker
4/19/2007 10:54:11 PM
DIRECTOR

Secondary Review and acting Deputy Director Memo for NDA 21-951
Cip-Isotretinoin

Submission date: 6/27/05

CDER Stamp date: 7/1/05

Applicant: Cipher Pharmaceuticals, Ltd.

Indication sought: severe recalcitrant nodular acne

The applicant has requested approval for Cip-isotretinoin capsules (10, 20, and 30 mg) for the treatment of severe recalcitrant nodular acne. In support of this indication, the applicant has submitted data from eight human pharmacokinetic (PK) studies: six single-dose and two multi-dose studies. The application was filed under section 505 (b) (2) of the US Federal Food, Drug and Cosmetic Act.

Safety

The applicant did not conduct clinical trials to determine the safety of their product. Instead, the applicant asserts to have established a biobridge between their product, Cip-isotretinoin, and the listed drug Accutane, in order to rely upon the Agency's finding of safety for the listed product. The inadequacy of the biobridge and the implications of that inadequacy will be discussed below.

Despite the absence of clinical trial data in the application, limited safety information was gleaned from the two 11-day multiple-dose clinical pharmacology studies. Please see the excellent review by Dr. Denise Cook for a full discussion of the safety data from those studies. Of note, three subjects were withdrawn from the multi-dose PK study because of psychiatric adverse events; all three subjects were receiving Cip-isotretinoin at the time the adverse events occurred. No subjects withdrew for psychiatric adverse events while receiving Accutane. Although the number of subjects (33) enrolled in the study was too small to draw meaningful conclusions, nonetheless the withdrawal of three subjects from the Cip-isotretinoin arm for psychiatric adverse events during the short dosing interval (11 days) is concerning.

Efficacy

The applicant did not conduct clinical trials to determine the efficacy of their product. Instead, the applicant claims to have established a biobridge between their product, Cip-isotretinoin, and the listed drug Accutane, in order to rely upon the Agency's finding of safety and effectiveness for Accutane.

Bioavailability

The reader is referred to the Clinical Pharmacology and Biopharmaceutics Review by Dr. Dennis Bashaw.

Cip-isotretinoin is bioinequivalent to Accutane. In the fasted state, both AUC and C_{max} are approximately two-fold greater for Cip-isotretinoin than for Accutane. In the fed state, after a high-fat meal, exposure is comparable. These results are summarized in the table below, taken from Dr. Bashaw's review:

Summary Results
Study 627-Pivotal Bioequivalency Study
(baseline adjusted)

Parameter	Treatment		Means		Type	Code	Ratio (%)	90% CI (%)
	Type	Trt*	Arithmetic (CV%)	Geometric				
AUC _t (ng·h/mL)	T - Fast	A	4307.77 (29)	4110.64	T: Food Effect	B vs. A	152.07	142.49 – 162.29
	T - Fed	B	6400.04 (20)	6251.05	R: Food Effect	D vs. C	263.46	246.86 – 281.17
	R - Fast	C	2349.24 (29)	2245.49	T/R - Fast	A vs. C	183.06	171.53 – 195.37
	R - Fed	D	6145.81 (26)	5915.87	T/R - Fed	B vs. D	105.67	99.01 – 112.77
AUC _{inf} (ng·h/mL)	T - Fast	A	4676.08 (28)	4470.45	T: Food Effect	B vs. A	149.78	140.52 – 159.66
	T - Fed	B	6858.70 (21)	6695.87	R: Food Effect	D vs. C	252.60	236.98 – 269.26
	R - Fast	C	2619.26 (30)	2500.01	T/R - Fast	A vs. C	178.82	167.76 – 190.60
	R - Fed	D	6561.62 (26)	6315.15	T/R - Fed	B vs. D	106.03	99.47 – 113.02
C _{max} (ng/mL)	T - Fast	A	347.00 (35)	323.18	T: Food Effect	B vs. A	134.39	122.60 – 147.32
	T - Fed	B	466.43 (38)	434.33	R: Food Effect	D vs. C	267.53	244.05 – 293.28
	R - Fast	C	169.66 (29)	161.43	T/R - Fast	A vs. C	200.20	182.63 – 219.46
	R - Fed	D	471.32 (41)	431.88	T/R - Fed	B vs. D	100.57	91.74 – 110.24

*A=Cipher Fasted, B=Cipher Fed, C=Accutane™ Fasted, D=Accutane™ Fed

Source: OCBP review by Dr. Dennis Bashaw, p.5.

The Agency has historically used fasted studies for bioequivalence determination. Assessment of pharmacokinetics following ingestion of high fat meal (as opposed to a moderate- or low-fat meal) provides a picture of the maximal food effect on systemic drug availability. Because of the serious safety risks associated with isotretinoin, as well as the significant difference between fed and fasted bioavailability for this moiety, other isotretinoin products approved via the 505(j) pathway have been required to demonstrate bioequivalence to Accutane in both the fasted and fed (high-fat) states, providing confidence that the generic drug product is bioequivalent to Accutane across the range of conditions likely to be encountered in real-world use (fasted, skipped meal, low-fat meal, moderate-fat meal, high-fat meal).

Insufficiency of the Biobridge

The DOSAGE AND ADMINISTRATION section of the Accutane package insert states, “Accutane should be administered with a meal.” It does not state that Accutane *must* be administered with a meal, nor does it specify that the meal should be high in fat. Real world use for isotretinoin, which is dosed BID, likely lies somewhere between the fed/fasted extremes of pharmacokinetic studies, with patients taking their medicine with low and moderate-fat meals, as well as on an empty stomach or with a high-fat meal on occasion. Because of this, establishment an adequate biobridge necessitates demonstration of comparable bioavailability in both the fed and fasted state. In the absence of such a biobridge, clinical trials are needed to establish safety and effectiveness for Cip-isotretinoin.

Bioequivalence is not required for 505(b)(2) applications. However, the sponsor must demonstrate the safety and effectiveness of their product. In the application, the applicant has submitted single and multiple dose PK studies to establish a biobridge to borrow the Agency's finding of safety and effectiveness for Accutane. Although the fed state shows comparable bioavailability for Cip-isotretinoin and Accutane, under fasted conditions Cip-isotretinoin is more bioavailable; both Cmax and AUC are higher for Cip-isotretinoin than for Accutane.

In real-world conditions, it is likely that most doses of Cip-isotretinoin would not be ingested with a high-fat meal, and hence exposure to the active moiety would be greater for this product than for Accutane. In the draft Guidance for Industry: Applications Covered by Section 505(b)(2), it states,

Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery¹

Elsewhere the Guidance advises, "For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product."

For a product such as isotretinoin, which has a narrow risk-benefit ratio and is associated with numerous serious adverse events such as depression, suicide, decreased bone mineral density, and teratogenesis, it is necessary to demonstrate that increased exposure to the drug as a result of increased bioavailability does not result in a worse safety profile. This is particularly important for neuropsychiatric adverse events, the pathophysiology of which is not clear. That is, it is not known whether the incidence of neuropsychiatric adverse events would increase with higher Cmax and AUC values, or higher steady-state exposures. Throughout the development of their product, beginning with their initial IND submission and repeated at each meeting with the Agency, the applicant was advised of the need for clinical studies to establish the safety and efficacy of Cip-isotretinoin, should Cip-isotretinoin show a different PK profile than Accutane.

505(b)(2) vs. 505(j) Pathway

The applicant chose to submit their application under Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act. However, the applicant has not identified any meaningful difference (e.g., food independence, once-a-day dosing, etc.), other than bioinequivalence, between their product and the reference drug, Accutane. The argument

¹ Guidance for Industry: Applications Covered by Section 505(b)(2) DRAFT GUIDANCE. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); October 1999, pp5-6. <http://www.fda.gov/cder/guidance/2853dft.pdf>

can be made that this application represents a presumptively-failed 505(j) application seeking approval through the 505(b)(2) mechanism.

However, since the applicant has chosen to submit their application under Section 505(b)(2) rather than 505(j), clinical trials data to establish the safety and efficacy of their drug are necessary. The Draft Guidance anticipates the scenario in which a product is bioinequivalent to the listed product and establishes the safety and efficacy through clinical trial data:

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), ***because approval will require the review of clinical data*** (emphasis mine). However, section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9))².

It appears that the only reason that this application was not submitted under Section 505(j) is that the drug is not bioequivalent to the listed product.

Summary

The applicant has submitted a 505(b)(2) application for Cip-isotretinoin and has attempted to establish a biobridge to Accutane in order to borrow the Agency's findings of safety and efficacy for the listed product. The applicant has provided data from single- and multiple-dose pharmacokinetic studies to support that bridge. The PK studies demonstrate bioinequivalence between the test and reference product, with increased exposure to Cip-isotretinoin in the fasted state as demonstrated by greater C_{max} and AUC values. Because of the serious adverse events associated with isotretinoin, demonstration of safety and efficacy of Cip-isotretinoin, in the absence of bioequivalence to Accutane, has not been established; therefore clinical trial data is necessary.

Regulatory Recommendation

Recommend non-approval. An approvable action was considered; however, because of the paucity of data submitted and the relative enormity of data still required, it does not appear that this application, "substantially meets the requirements"³ for approval nor could be described as, "about to be approved"⁴.

Outstanding Informational Needs

Clinical data regarding the safety and efficacy of Cip-isotretinoin are necessary. Two avenues for provision of this information are proposed:

1. Clinical trial comparing the safety and efficacy of Cip-isotretinoin to Accutane in patients with severe, recalcitrant nodular acne.

² Guidance for Industry: Applications Covered by Section 505(b)(2) DRAFT GUIDANCE. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); October 1999, pp3-4. <http://www.fda.gov/cder/guidance/2853dft.pdf>

³ 21CFR314.110(a), 2005; p.141.

⁴ Ibid., p.141.

2. Population PK trial in a sufficient number of subjects (>200 per arm) and of a sufficient duration (dosed for a full clinical course of 20 weeks) to demonstrate that the levels of test and reference product are similar under real-world conditions, and also to provide safety and efficacy data.

Jill Lindstrom, MD

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this page is the manifestation of the electronic signature.**

/s/

Jill Lindstrom
4/26/2006 05:57:22 PM
MEDICAL OFFICER

Stanka Kukich
4/27/2006 08:43:13 AM
MEDICAL OFFICER

Concur with Deputy Director Memo, however, would recommend approvable
action once the deficiencies outlined in the action
letter are resolved

CLINICAL REVIEW

Application Type NDA
Submission Number 21-951
Submission Code 000

Letter Date 6/27/05
Stamp Date 7/1/05
PDUFA Goal Date 5/1/06

Reviewer Name Denise Cook, M.D.
Review Completion Date 4/25/06

Established Name Isotretinoin
(Proposed) Trade Name Cip-Isotretinoin
Therapeutic Class Oral Retinoid
Applicant Cipher Pharmaceuticals, LTD

Priority Designation S

Formulation Oral
Dosing Regimen 0.5 mg/kg/day – 2.0 mg/kg/day
Indication Severe Recalcitrant Nodular Acne
Intended Population Ages 12 - Adult

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that NDA 21-951, for oral isotretinoin (Cip-Isotretinoin) capsules, 10 mg, 20 mg and 40 mg, for the treatment of severe, recalcitrant nodular acne should be a "non-approvable". The application was submitted as a 505(b)(2) with Accutane as the reference listed drug. On review of the application, the applicant has failed to demonstrate an adequate bridge of safety and efficacy for their product, Cip-Isotretinoin.

Non-approvable is recommended for the following reasons:

1. The different PK profile of Cip-Isotretinoin does not allow for extrapolation of primarily the safety profile of Accutane and does not guarantee efficacy, either. Since Accutane has a myriad of serious adverse events that can occur during treatment, this difference in PK profile, in the absence of a clinical trial, makes the risk/benefit analysis for this product unacceptable for marketing.

2. The signal from the small safety data base obtained from one of the multi-dose PK studies underscores the need for further study of this drug product.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

There were no clinical studies conducted under this NDA. The only clinical data obtained was safety data from 2 small multi-dose PK studies of 11 days duration.

1.2.2 Efficacy

As no clinical trials were conducted, no efficacy data was generated for this drug product. In this reviewer's opinion, the exact nature of the efficacy of Cip-Isotretinoin is not known. Certainly, one might surmise that since higher levels of Cip-Isotretinoin are achieved under fasted conditions, and subjects are not likely to take the medication with a high fat meal for 20 weeks, that the efficacy might be better. However, this is not certain, for higher blood levels do not always translate into higher efficacy but usually translates into higher toxicity. Given that Accutane cures 80% of subjects who are treated for severe, recalcitrant nodular acne, any additional efficacy would have to be weighed very carefully against additional toxicity. The

absence of a clinical trial against Accutane (the RLD) in this application makes this analysis impossible.

1.2.3 Safety

There were two multi-dose biopharm studies, study #666 and study #442. Both studies were 11 days duration, in house, and compared different doses of Cip-Isotretinoin to Accutane in healthy subjects. The safety data base is small, 47 subjects in study 666, and 36 subjects in study 444. Most of the adverse events were classified as mild to moderate in severity.

The top 10 adverse events were those that would be expected from use of oral isotretinoin and were fairly similar between the two drug products. The data suggested that Cip-Isotretinoin might cause less alteration in liver function. However, the most concerning safety data from these studies involves the incidence of neuropsych events that occurred during trial 442 that required discontinuation from the study. There were 3 such instances and all 3 patients were on Cip-Isotretinoin. With such a small data base, one cannot conclude that this drug product may have more neuropsych events than Accutane, but it is a signal that cannot be ignored and should be confirmed or denied by a clinical trial.

1.2.4 Dosing Regimen and Administration

The sponsor is requesting the same dosing and administration as that of Accutane. That is, that the drug should be given in a dose from “0.5 mg/kg/day to 1.0 mg/kg/day in two divided doses with food for 15 – 20 weeks.”

1.2.5 Drug-Drug Interactions

No drug-drug interactions were studied in this NDA.

1.2.6 Special Populations

The applicant asked for a waiver for the pediatric population. A waiver can be granted for patients less than 12 years of age, as severe, nodular acne does not occur in this age group. Patients 12 years and older will need to be incorporated into any clinical trial conducted to seek approval for Cip-Isotretinoin.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.11 Description of the Product

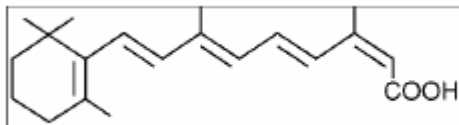
Isotretinoin, a retinoid, is available as CIP-ISOTRETINOIN in 10 mg, 20 mg and 30 mg gelatin capsules for oral administration. Each capsule contains isotretinoin, stearoyl macrogol glycerides, soybean oil, sorbitan monooleate, propyl gallate, gelatin, titanium dioxide and iron oxide.

2.12 Established Name and Proposed Trade Name

The established name of the drug product is isotretinoin. The proposed trade name is Cip-Isotretinoin. The product will be referred to as Cip-Isotretinoin throughout this review.

2.13 Chemical Class

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



2.14 Pharmacological Class

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

2.15 Proposed Indication, Dosing Regimen, Age Groups

Indication

CIP-ISOTRETINOIN is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become supportive or hemorrhagic. “Severe,” by definition², means “many” as opposed to “few or several” nodules. Because of significant adverse effects associated with its use, CIP-ISOTRETINOIN should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, CIP-ISOTRETINOIN is indicated only for those

females who are not pregnant, because CIP-ISOTRETINOIN can cause severe birth defects (see boxed CONTRAINDICATIONS AND WARNINGS).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.^{1,3,4} If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off CIP-ISOTRETINOIN. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (b) (4)

(b) (4)

Reviewer's Comment: *This entire section is predicated on Cip-Isotretinoin's ability, through a 505(b)(2) route, to borrow the FDA's findings of safety of Accutane, the reference listed drug product. The sponsor did not perform any clinical studies to ascertain the safety of Cip-Isotretinoin, which is not bioequivalent to Accutane in either the fed or fasted state.*

2.2 Currently Available Treatment for Indications

The best currently available treatment for severe, recalcitrant nodular acne is Accutane and its generics, three which are currently marketed, Amnesteem, Claravis, and Sotret. The generic products were required to be bioequivalent to Accutane in both the fed and fasted state.

Accutane and its generics cure the disease in 80% of patients after one 20-week course of treatment with doses that range from 0.5 mg/kg/day – 1.0 mg/kg/day. Rarely are higher doses needed, but the products are approved for up to 2mg/kg/day. Less than 20% of patients who fail need a second course of treatment. Some of these patients may exhibit a milder form of acne which is amenable to topical treatment and/or possibly systemic antibiotics.

2.3 Availability of Proposed Active Ingredient in the United States

Isotretinoin is readily available in the United States.

2.4 Important Issues With Pharmacologically Related Products

Isotretinoin, as a class of products, is approved under Subpart H in the United States because it is a potent human teratogen. It also causes a myriad of serious side effects. Neurological/psychiatric adverse events include mood alteration, violent behavior, depression, and suicide. Central nervous system effects include pseudotumor cerebri, CNS developmental abnormalities, and headaches. Other organ systems that can be affected include lipid alterations with elevations of serum triglycerides which has led to acute pancreatitis in some cases, and to a lesser extent elevations in serum cholesterol; increases in liver function tests, including hepatitis; hearing impairment; vision impairment; musculoskeletal effects which have included decreases in bone mineral density, delayed healing of bone fractures, and premature epiphyseal closure; and inflammatory bowel disease in patients without a pre-existing history.

2.5 Presubmission Regulatory Activity

- PreIND Meeting – July 16, 2001
 - Sponsor proposed to conduct PK studies and a single phase 2/3 clinical trial to support a 505(b)(2) application
 - Advice from Agency
 - phase 2 dose ranging study

- phase 3 trial comparing Cip-isotretinoin either bid or q day or both to Accutane bid
- Original IND (b) (4) – June 7, 2002
 - The sponsor was advised, “The clinical benefit of increased bioavailability is unclear unless it involves food independence.”
 - “It is highly unlikely that PK studies will support the safety and efficacy of dosing equivalent to Accutane.”
 - “We strongly support clinical testing of once daily dosing vs. BID dosing.”
 - “If a comparable dose of Accutane (based on data from your PK studies) was included in a third arm, this one well-powered trial, combined with data from the P2 study, *might* allow comparative safety and efficacy labeling.
- Guidance Meeting – May 21, 2003
 - Sponsor was advised to explain lack of dose proportionality for their drug product
 - Advised, “If any of the dosage sizes are found to be more bioavailable than the same size capsule of Accutane, (for example, 10 mg) then clinical trials will be necessary.”
- Guidance Meeting – April 28, 2004
 - Sponsor was advised, “From a bioequivalence standpoint, the pivotal in vivo bioequivalency trials are considered to be those under fasted conditions.”
 - “Any considerations that could be perceived as an advantage with the Cipher product should be demonstrated and proven clinically.”

3 CLINICAL PHARMACOLOGY

The pharmacokinetic data will be very briefly summarized here. The source for this section is from the clinical pharmacology and biopharmaceutics review by Dr. Dennis Bashaw. The reader is referred to that review for more details.

There were 8 in vivo pharmacokinetic studies submitted to the NDA in support of Cip-Isotretinoin. Six of the studies were single-dose studies and 2 were multi-dose studies. The majority of the single-dose studies were done under fed conditions. Two studies were done under both fed and fasted conditions. As part of a 505(b)(2) application, Cip-Isotretinoin was compared to Accutane.

The data demonstrated a lack of dose proportionality between strengths of Cip-Isotretinoin. Dr. Bashaw found this disturbing, as the formulation uses varying amounts (b) (4) for each strength, and thus, the capsules should be dose proportional. He further concluded that this represents a problem, as interchange between dosage units is not possible and there would be a difference in exposure related to how it is dosed (e.g. 2 x 10 mg vs. 1x 20 mg).

Dr. Bashaw found, in review of the PK data, that Cip-Isotretinoin is not bioequivalent to Accutane. Under fed conditions, using a high-fat meal, the data demonstrated that the

pharmacokinetic profile of the 20 mg and 30 mg capsules of Cip-Isotretinoin are equivalent to Accutane when compared to AUC (values are within the 90% confidence intervals) but not to C_{max} (values fall outside the 90% confidence intervals: lower). There is also a marked difference between the two products under fasted conditions. Cip-Isotretinoin is more bioavailable than Accutane under fasted conditions, thus exhibiting a “relatively” reduced food effect. Dr. Bashaw concluded in his review, “This finding of C_{max} inequivalence, coupled with that of the lack of a demonstration of fasted bioequivalence, highlights the need of clinical studies to demonstrate the true nature and impact of the observed differences.” Dr. Bashaw finally recommends that the sponsor perform a large population PK study in an attempt to resolve these issues surrounding dose and plasma level differences between Cip-Isotretinoin and Accutane. However, if not resolved by a population PK study, a clinical trial will be necessary.

4 INTEGRATED REVIEW OF SAFETY

4.1 Methods and Findings

As stated above in the clinical pharmacology section, there were not any clinical trials submitted in this NDA, only biopharm studies. However, there were 2 multi-dose biopharm studies that were 11 days in duration. From these studies, some safety data can be obtained. This will be detailed in this section.

There were two multi-dose biopharm studies, study #666 and study #442. Both studies were 11 days duration, in house, and compared different doses of Cip-Isotretinoin to Accutane in healthy subjects. The safety data base is small, 47 subjects in study 666, and 36 subjects in study 444. Most of the adverse events were classified as mild to moderate in severity.

Table 1
Disposition of Subjects

Study	Age	Subjects Completed	Subjects Discontinued*
666	19-49 years old Mean – 36 years old	40	5
442	20-54 years old Mean – 35 years old	28	5

* Discontinuations were due to an adverse event

4.1.1 Deaths

There were no deaths in these two studies.

4.1.2 Dropouts and Other Significant Adverse Events

There were 6 discontinuations because of adverse events in study 666. These were evenly distributed between Cip-Isotretinoin and the reference listed drug, Accutane. There were 5 discontinuations because of adverse events in study 442. All of these occurred in the Cip-Isotretinoin arm. All but one of these discontinuation was “dismissed” by the investigator because of the adverse event. Subject #37 in study 666 withdrew from the study.

In addition, in study 442, there were 3 patients in the Cip-Isotretinoin arm that reported euphoria, “feeling stoned” compared to one patient describing such a feeling in the Accutane arm.

4.1.3 Overall profile of dropouts

As far as can be ascertained from CRFs and the NDA, the patients with psychiatric adverse events who were dismissed from study 442 did not have a previous history of psychiatric problems.

4.1.4 Adverse events associated with dropouts

Table 2
Discontinuations Study 666

Drug	Patient #	Adverse Event
Cip-Isotretinoin 2 x 20 mg BID	2	Headache
	26	Abdominal pain; Left eye pain
	36	Musculoskeletal pain/ increased triglycerides
Accutane 40 mg BID	15	Vomiting; increased LFTs
	37	Headaches; acne; tingling sensation both arms
	41	Swelling of both eyelids with pruritus

Source: Sponsor’s submission, NDA 21-951, Module 5 Volumes 1.136 and 1.137

Table 3
Discontinuations Study 442

Drug	Patient #	Adverse Event
Cip-Isotretinoin 30 mg QD	10	Diarrhea; abdominal cramps; emesis
	20	Rash
	6	Emotional labile; agitation; insomnia; less social; punched walls which resulted in swollen hands and necessitated a hospital visit; cleared by psych
	13	Irritation and “momentary” (91 hours) desire (rage) to hurt people
	26	Non-compliance; agitated; threw food in garbage on day 8; euphoria; weakness
Accutane 40 mg QD	No discontinuations because of adverse events	

Source: Sponsor’s submission, NDA 21-951, Module 5, Volume 1.138; Module 5 section 3, page 34

4.1.5 Common Adverse Events

The following tables list the top ten common adverse events from both study 666 and 442. These are events that are expected in patients that take isotretinoin. Although not in the top 10 adverse events, each drug did have a subject with elevated triglyceride levels.

Table 4
Top 10 ADRs – Study 666

Cipher 2x20mg BID N =		Accutane™ 40mg BID N =	
dry lips (26)		headache (36)	
headache (25)		dry lips (31)	
dry skin (9)		dry skin (13)	
diarrhea (7)		metallic taste in mouth (6)	
dry skin on face (4)		elevated ALT (6)	
nose bleed (4)		elevated AST (5)	
elevated blood pressure (3)		elevated blood pressure (4)	
sore throat (3)		eye irritation (4)	
dry and cracked lips (2)		elevated gamma GT (3)	
flatulence (2)		diarrhea (3)	
Total:	128	Total:	174
Adapted from biopharm review			

Table 5
Top 10 ADRs – Study 442

Cipher 30mg QD N =		Accutane™ 40mg QD N =	
headache (11)		headache (10)	
dry skin (10)		pain (8)	
pruritus (9)		dry mouth (8)	
dry mouth (7)		rash (9)	
rash (6)		pruritis (5)	
asthenia (6)		dry skin (4)	
headache intermittent (4)		asthenia (4)	
acne (3)		insomnia(4)	
conjunctivitis (3)		conjunctivitis (4)	
nose bleed (3)		constipation (3)	
Total:	127	Total:	126

4.1.6 Additional Submissions, Including Safety Update

The 120 day safety update was received by the Agency on November 7, 2005. The sponsor reported that there was not any new safety information to report. However, they do report that there were not any reports of pregnancies during the 4 week post study monitoring period.

4.2 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

These in vivo PK studies were not powered to analyze safety and thus it is difficult to make conclusions regarding the safety profile of Cip-Iso tretinoin with a definite degree of certainty. The safety data base is also very small, with only 83 subjects taking medication over 11 days, which is much shorter than the 20-week duration of treatment with isotretinoin for this indication. Thus, this is a very important limitation of the data and conclusions derived from this data.

It appears from the safety data collected that many of the adverse events that are associated with Accutane also occur with Cip-Iso tretinoin. These include but are not limited to mucocutaneous adverse events, alteration in lipid metabolism, elevated blood pressure, and gastrointestinal events. It may be from this limited data, that Cip-Iso tretinoin may not cause alterations in liver functions to the same degree as Accutane.

However, the most concerning safety data from these studies involves the incidence of neuropsych events that occurred during trial 442 that required discontinuation from the study. There were 3 such instances and all 3 patients were on Cip-Iso tretinoin. With such a small data base, one cannot conclude that this drug product may have more neuropsych events than Accutane, but it is a signal that cannot be ignored and should be confirmed or denied by a clinical trial.

5 ADDITIONAL CLINICAL ISSUES

5.1 Pediatrics

The sponsor is requesting a waiver for all pediatrics studies. At the present time, this can only be granted for those below the age of 12, as severe, recalcitrant nodular acne does not occur in those ages. An adequate safety bridge between Cip-Iso tretinoin and Accutane has not been established in adults as this drug product is not bioequivalent to Accutane. Thus, pediatric studies in subjects greater than or equal to 12 years of age may be required to assess the safety and efficacy of Cip-Iso tretinoin.

5.2 Postmarketing Risk Management Plan

As this drug product will be non AB rated, if ever approved, the current iPLEDGE pregnancy prevention program will not accommodate this drug product. Thus, a second iPLEDGE-like program will have to be developed by the sponsor prior to approval.

6 OVERALL ASSESSMENT

6.1 Conclusions

Cip-Isotretinoin is a new formulation of isotretinoin that was submitted under a 505(b)(2) with Accutane as the reference listed drug product. The sponsor, through PK studies, wants to establish a bridge for the findings of safety and efficacy of Accutane to their product. The sponsor was informed in several meetings with the Agency, that given the nature of Accutane's safety profile, PK studies alone would be inadequate if there was any difference in the PK profile of Cip-Isotretinoin capsules and Accutane capsules.

Pharmacokinetic data reveal that Cip-Isotretinoin is not bioequivalent to Accutane in either the fed or fasted state. In the fasted state, on a high fat diet, Cip-Isotretinoin is bioequivalent for AUC but not for C_{max}. More importantly, in the fasted state, Cip-Isotretinoin is much more bioavailable than Accutane. This is of importance because in the real world, it is unlikely that a high fat diet, such as the one used in the studies, will be consumed by the patient twice a day for 20 weeks (the course of treatment). Teenagers and young adults are more likely to eat a sparse breakfast, if indeed, they eat breakfast at all. Thus, patients taking Cip-Isotretinoin, most likely will be exposed to higher levels of isotretinoin, and potentially more serious adverse events.

The Agency has some experience with another formulation of isotretinoin, Accutane NF, which is more bioavailable, and can be taken without regard to food. In a clinical trial, it was found that there were more neuropsych events in the Accutane NF arm than in the Accutane arm, 11:1, and that discontinuations for a neuropsych event occurred only in the Accutane NF arm. This NDA was given an "approval" action, pending more clinical data to explain this difference. In this NDA, there were 3 neuropsych events that resulted in dismissal from the trial and all 3 patients were taking Cip-Isotretinoin, 30 mg q day at the time of the adverse event. Even though, as mentioned elsewhere in the NDA, the PK studies were not designed to look at safety, this is a signal that cannot be ignored and further study is necessary to ascertain the true nature of the adverse event profile of Cip-Isotretinoin.

In conclusion, Cip-Isotretinoin is not bioequivalent to Accutane. In essence, it has a different PK profile compared to Accutane. Thus, the safety and efficacy of this drug product compared to Accutane is unknown. There may be a high probability of increased neuropsychiatric events and if the efficacy is decreased, this could also represent a safety concern for females of childbearing potential and teenagers and young adults if they have to take a second course of the drug product. This would increase the exposure to a human teratogen for the former group and increase exposure to long term effects of isotretinoin on bone in all groups, for example. Given

the serious nature of adverse events that can occur in patients who take Accutane, the known is that Cip-Isotretinoin offers no public health advantage either in terms of once daily dose or food independence. And because it has a different PK profile from Accutane and because of an absence of a clinical trial comparing Cip-Isotretinoin to Accutane, the sponsor has failed to provide an adequate bridge of safety to their product, Cip-Iostretinoin. The efficacy and safety of this drug product as it compares with Accutane is unknown.

6.2 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that the Cip-Isotretinoin NDA receives a “non-approvable” action.

The applicant should conduct a clinical trial with a sufficient number of patients to detect an incidence of an adverse event occurring in 1% of the population for safety. This trial should be a head-to- head trial with Accutane. Efficacy should be ascertained in this trial, also, as Cip-Isotretinoin should be non-inferior to Accutane. The applicant will also need to develop and present in any future NDA, a plan to incorporate their drug product into the iPLEDGE riskMAP.

6.3 Comments to Applicant

The applicant may wish to consider the following:

1. A phase 3 safety and efficacy trial in patients with severe, recalcitrant nodular acne where Cip-Iostretinoin is compared to Accutane at a dose of 1.0 mg/kg/day. This trial should have a sufficient number of patients, in all age groups in which the disease occurs, to detect an incidence of an adverse event occurring in 1% of the population for safety.

The following additional items, at a minimum, important for adequate labeling should be addressed in the same study:

- Prospective detailed delineation of psychiatric and CNS events by specialists, with attention to risk factors and response to intervention

- Adequate monitoring for bone mineral density changes and premature closure of the epiphyses
 - Adequate testing for hearing and vision impairment and follow-up to inform labeling regarding reversibility
 - Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility
2. The sponsor will have to present a plan to incorporate Cip-Isotretinoin into the iPLEDGE program.

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this page is the manifestation of the electronic signature.**

/s/

Denise Cook
4/25/2006 01:59:19 PM
MEDICAL OFFICER

Jill Lindstrom
4/26/2006 05:50:25 PM
MEDICAL OFFICER

Stanka Kukich
4/27/2006 08:34:07 AM
MEDICAL OFFICER

Concur with MO review, however, would recommend approvable action
once the deficiencies outlined in the action letter
are resolved