CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021951Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 24th, 2012
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA	21-951
Applicant Name	Cipher Pharmaceuticals Inc.
Date of Submission	November 29th, 2011
PDUFA Goal Date	May 29th, 2012
Proprietary Name /USAN	Absorica™ / isotretinoin
Dosage Forms / Strength	Capsules/ 10mg, 20mg, 30mg, 40mg
Proposed Indication	Severe recalcitrant nodular acne
Action	***Approval***

Material Reviewed/Consulted Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Denise Cook, MD / Gordana Diglisic, MD
Cross Discipline Team Leader	Gordana Diglisic, MD
Statistical Review	Yuqing Tang, PhD / Mohamed Alosh, PhD
Pharmacology Toxicology Review	Jiaqin Yao, PhD / Barbara Hill, PhD
Chemistry, Manufacturing, Controls	Tarun Mehta, M.Sc / Shulin Ding, PhD
CMC Biopharmaceutics	Minerva Hughes, PhD / Angelica Dorantes, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD / Doanh Tran, PhD
Pharmacometrics	Dhananjay Marathe, PhD / Yaning Wang, PhD
Office of Prescription Drug Promotion	Lynn Panholzer, PharmD / Sheetal Patel, PharmD
OSE/Division of Medication Error Prevention and Risk Management	Teresa McMillan, PharmD / Lubna Merchant, PharmD / Carol Holquist, RPh
OSE/Office of Medication Error Prevention and Risk Management	Reema Mehta, PharmD, MPH / Kendra Worthy, PharmD / Claudia Manzo, PharmD
Study Endpoints and Labeling Dev.	Eric Brodsky, MD / Laurie Burke, RPh, MPH
Office of Medical Policy/Division of Medical Policy Programs	Latonia Ford, RN, BSN, MBA / Barbara Fuller, RN, MSN, / LaShawn Griffiths, MSHS-PH, BSN, RN,
Center for Devices and Radiologic Health	James Kane, PhD / Srinivas Nandkumar, PhD
Division Reproductive and Urologic Products Consult	Stephen Voss, MD / Theresa Kehoe, MD/ Audrey Gassman, MD
Division of Transplant and Ophthalmology Products Consult	William Boyd, MD / Wiley Chambers, MD
Pediatric and Maternal Health Staff Consult	Carrie Ceresa, PharmD, MPH / Melissa Tassinari, PhD, DABT / Lisa Mathis, MD
Division of Psychiatry Products	G. Dubitsky, MD / J. Zhang, MD / T. Laughren, MD

OSE-Office of Surveillance and Epidemiology

Signatory Authority Review

1. Introduction

NDA 21-951 was originally submitted in 2005 as a 505(b) (2) application containing pharmacokinetic studies. In 2006 and 2007 approvable letters were issued, based upon lack of evidence demonstrating that the bioinequivalence between Absorica™ and the listed product was clinically insignificant. This application provides additional information to support the safety and efficacy of Absorica™. I am in agreement with the recommendation of the review team that the product be approved. There are no areas of disagreement between reviewers and no issues that preclude approval.

2. Background

Isotretinoin for the treatment of nodular acne was originally approved in 1982 as Accutane®. In 2002, the first generic products were approved, and there are now multiple marketed generics. The innovator product, Accutane®, was withdrawn from the market in 2009. Absorbica™ is bioinequivalent to approved isotretinoin, and therefore does not meet the criteria for an abbreviated new drug application (ANDA).

On July 27th 2005, Cipher Pharmaceuticals submitted original NDA 21-951 for their isotretinoin product, Absorica™, and proposed approval under 505(b)(2) for the treatment of severe recalcitrant nodular acne. Under fed conditions, Absorica™ has a similar rate and extent of systemic exposure as that of Accutane®, however, under fasted conditions administration of Absorica™ results in higher average blood levels over the course of therapy. It was determined that clinical trial data would be needed to evaluate safety concerns potentially associated with the increased total isotretinoin exposure following administration of Absorica™ when compared to Accutane®, due to the overall greater bioavailability of Absorica™.

The clinical development program of Absorica™ took into account the relevant guidelines and regulatory and scientific advice obtained from FDA. The study design, efficacy endpoints, safety endpoints, and statistical issues were discussed with the FDA during a series of meetings, and related correspondence. The study protocol was submitted to the Investigational New Drug (IND) application prior to study initiation, and agreement with the Agency on study design was achieved through the Special Protocol Assessment (SPA) process.

3. CMC

Isotretinoin is a very poorly water-soluble compound and absorption following oral administration is reduced in the fasting state. The applicant has used a formulation technology (b) (4) consisting of a hard gelatin capsule containing the drug substance (b) (4) . The chemistry reviewers, Tarun Mehta, M.Sc and Minerva Hughes, PhD have concluded that the application has provided adequate information to assure the identity, strength, quality and purity of the drug substance. The drug product will be approved in 10mg, 20mg, 30mg and 40mg capsules. The physico-chemical and pharmacokinetic information provided supports a drug product dosage form classification as Immediate Release (IR). The dissolution profiles generated using the proposed dissolution method are highly variable. FDA and the applicant have agreed on the interim dissolution method and acceptance criteria for the release and stability studies, with the applicant's commitments to further post approval studies with the production batches. The applicant has agreed to a post marketing commitment to conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. 36 month stability information has been provided for the 10-20-30mg strengths, and 24 month stability for the 40mg strength.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. The applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

There have been no pharmacology/toxicology concerns raised by this application.
I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The bioavailability of Absorica™ and the potential impact of the bioinequivalence in comparison with marketed isotretinoin have been the subject of multiple agency reviews for this application. These include reviews by Dennis Bashaw, Ph.D. and Chinmay Shukla, PhD. The applicant conducted relative bioavailability (BA) trials with their product and the listed drug (Accutane®) under fasting and fed conditions and a food effect study. In addition, the applicant conducted studies to demonstrate proportionality between different strengths under fasting and fed conditions to support interchangeability among different strengths, and single and multiple dose PK estimations obtained by serial blood sampling. These studies were reviewed by Dr. Dennis Bashaw (dated 04/21/2006; 04/09/2007).

The results of relative BA trials showed that under fed conditions Absorbica™ was bioequivalent (BE) with Accutane®, but they were not BE under fasting conditions. Specifically, the exposure of Absorbica™ was approximately 2 fold higher than Accutane® when both the formulations were administered under fasting conditions. The relative BA trial was conducted using only the 20 mg strength of Absorbica™, but results of proportionality studies support application of these

findings to other strengths. The results of proportionality trials indicated that the bioavailability of Absorbica™ increased in a proportional manner between 10 mg and 30 mg strength under both fasting and fed conditions. The sponsor also conducted a dosage strength proportionality study between the 20 and 40mg strength under fasting and fed conditions. The results indicated that they were proportional under fed conditions, but under fasting conditions the exposure of the 40mg strength was slightly less proportional to the 20mg strength. The results of the food effect trial (using 30 mg strength), indicated that the effect of food was substantially larger on the Accutane® formulation compared to the Absorbica™; however, there was still a significant food effect on the Absorbica™. Another food effect study with the 40mg had similar results. In the presence of food, the systemic exposure (AUC) increased on average 1.5 times for Absorbica™ formulation and approximately 2.5 times for the Accutane® formulation. The peak exposure (C_{max}) to isotretinoin increased under fed conditions and was approximately 1.6 times and 2.7 times for Absorbica™ and Accutane® formulations, respectively, compared to fasting conditions.

A total of 13 biopharmaceutic studies have been conducted with Absorica™. Results of these studies comparing Absorica™ to Accutane® show that:

- Absorica™ and Accutane® are bioequivalent under high-fat fed conditions.
- Under fasted conditions, the bioavailability of Accutane® is approximately 60% lower than that observed under fed conditions, whereas the bioavailability of Absorica™ is approximately 30% lower than that observed under fed conditions;
- Absorica™ is dose proportional across the strengths 30 mg versus 3 x 10 mg and 40 mg versus 2 x 20 mg under fed conditions;
- The plasma levels of Absorica™ observed under fasted conditions do not exceed the threshold of absorption observed under fed conditions.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

Study ISOCT.08.01 supports the safety and efficacy of Absorica™ when used twice daily for 20 weeks for the treatment of severe recalcitrant nodular acne. The efficacy of isotretinoin is also supported by the bioavailability studies demonstrating that isotretinoin will be at least as bioavailable as the listed drug. The application did not propose, nor demonstrate, that the differential bioavailability is associated with improved efficacy.

The application relies upon previous Agency findings of safety and effectiveness for isotretinoin. The applicant submitted data from one trial, Study ISOCT.08.01, to compare the safety and efficacy of their product to the listed drug. The general study design, the co-primary endpoints, analysis population, statistical analysis methods and primary method of handling

missing data were in agreement with Agency comments.

A total of 925 subjects were randomized, 464 on Absorica™ and 461 on listed drug product isotretinoin. This was a multi-centered, prospective, randomized, active-controlled, parallel group, non-inferiority trial. Absorica™ was considered non-inferior to the listed product if: (1) the upper bound of the 2-sided 95% CI for the treatment difference (Absorica™ minus listed product) was ≤4 for the total nodular lesion count; and (2) if the lower bound of the 95% CI for the treatment difference (Absorica™ minus listed product) 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.

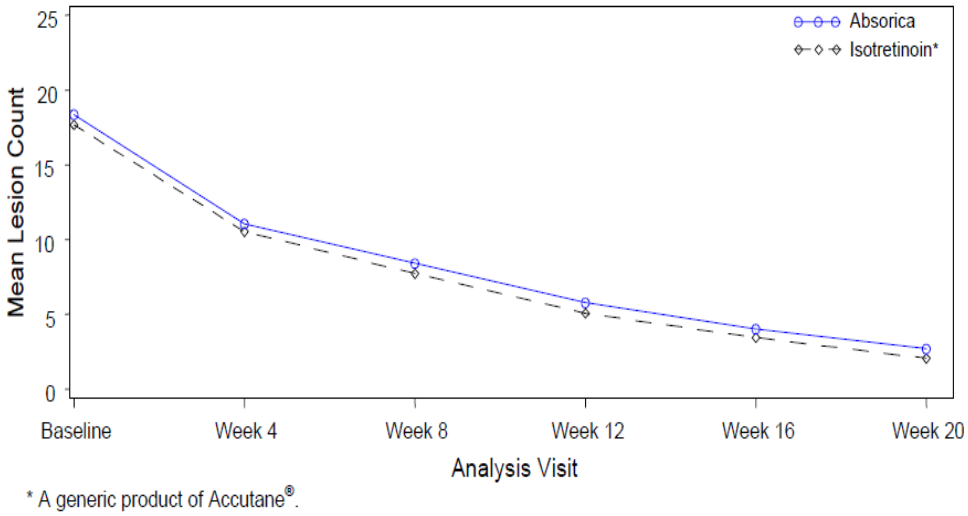
Change from Baseline to Week 20 in total nodular lesion count and proportion of patients with at least a 90% reduction in total nodular lesion count from Baseline to Week 20 are presented in below.

Efficacy Results at Week 20

	Absorbica ™ N=464	**Isotretinoin* N=461**
Nodular Lesions		
Mean Baseline Count	18.4	17.7
Mean Reduction	-15.68	-15.62
Patients Achieving 90% Reduction	324 (70%)	344 (75%)

*A generic product of Accutane®

Total Nodular Lesions Counts by Visit



* A generic product of Accutane®.

I concur with the conclusions of the biostatistician, Y Tang, PhD, and medical reviewer, D. Cook M.D. Absorica™ is not inferior to approved isotretinoin in the treatment of severe

recalcitrant nodular acne. There is no information to support any claims regarding the clinical effect of the bioavailability differences between Absorica™ and approved isotretinoin products.

8. Safety

The major objective of Study ISOCT.08.01 was to characterize the safety profile of Absorica™, which is more bioavailable in the fasting state than approved isotretinoin. While Absorica™ and approved isotretinoin are similarly bioavailable with meals, Absorica™ has increased systemic bioavailability when taken without meals. Evaluating the clinical impact, if any, of this bioinequivalence was the focus of Study ISOCT.08.01. I have reviewed the conclusions of Drs. Cook, Diglisic, and the specialty consultants and concur that there are no safety differences demonstrated between Absorica™ and approved isotretinoin.

Extensive discussions were held with the applicant to establish reasonable and measureable endpoints to inform the safety of Absorica™. The protocol included assessments of psychiatric adverse events (Columbia Suicide Severity Rating Scale, General Anxiety Disorder-7, Patient Health Questionnaire -8 assessment, psychosis assessment), eye disorders, bone mineral density and bone age changes (DEXA, hand X-rays, and Tanner staging), ear disorders (audiology testing in a subset of subjects at 25% of study sites), and laboratory studies. 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 were comprehensive and included hematology, serum chemistry, lipid profiles, and urinalysis. Safety data was also obtained through physical examinations, vital signs, and musculoskeletal assessments.

The safety population consisted of 924 subjects, 464 on Absorica™ and 460 on approved isotretinoin. Enrolled subjects were between the ages of 12 and 52 years, with 43% of the enrolled subjects < 18 years old. Approximately 60% of subjects in both arms were male, predominately white (87%). The two treatment groups were similar with respect to all parameters of treatment exposure and eighty seven percent (87.3%) received at least nineteen weeks of treatment.

Mental Health: I have reviewed the comprehensive consultation from Dr. Lubitsky, who concludes that the psychiatric assessments performed in study ISOCT.08.01 appear to be adequate and are consistent with recommendations provided by the Division of Psychiatry Products. There were no important differences noted between the psychiatric safety profiles of Absorica™ and approved isotretinoin. Therefore, labeling of reported psychiatric adverse events for Absorica™ capsules will be the same as approved isotretinoin.

Bone: I have reviewed the comprehensive consultation from Dr. Voss, who concludes that overall the study confirmed that bone safety concerns 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 Absorica™ and approved isotretinoin. Information from relevant sections of the approved isotretinoin product labeling will be incorporated into the Absorica™ labeling.

Audiology: Dr Kane has reviewed the audiology information, and concludes that the safety results from this evaluation for audiology changes are consistent with the information

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

Ophthalmology: I have reviewed the comprehensive consultation from Dr Boyd who concludes that the protocol did not provide adequate ocular monitoring of study subjects. His recommendation is that to evaluate ocular safety, the protocol would have needed to include assessments of the conjunctiva, cornea, lens, optic nerve, retina, color vision, dark adaptation, retinal electrical activity and tear production. Although flawed, there are no safety signals identified in ISOCT.08.01 which indicate that Absorica™ should not share ocular labeling consistent with other approved isotretinoin products. The review recommends that the general statements regarding isotretinoin products in the physician and patient labeling should be retained. Dr. Cook also concludes that these investigations did not observe any differences between the treatment groups and that the labeling for ocular events should be consistent with current isotretinoin labeling.

Laboratory Data: The most frequently reported abnormalities in both treatment groups were elevated CK levels, with marked elevation (flagged by the reporting laboratory- CK $\geq$ 350 U/L) being reported for 24% of subjects in the Absorica™ group and 23% of subjects in the approved isotretinoin group. There was no observed difference between Absorica™ and approved isotretinoin in the effect on lipid metabolism. In the differential white blood cell count, mean increases in the percent lymphocytes and monocytes and mean decreases in the percent neutrophils were observed over the course of the trial in both groups. Analysis of the laboratory data did not reveal any significant differences between Absorica™ and approved isotretinoin. These findings are consistent with current isotretinoin labeling and the physician labeling will be similar.

9. Advisory Committee Meeting

No advisory committee was held for this application, as there were no new issues or concerns to be discussed.

10. Pediatrics

The proposed indication, like for the listed drug, is “treatment of severe recalcitrant nodular acne in patient 12 years of age and older”. Because this is a 505(2) (b) application that relies for approval on the Agency’s finding of safety and effectiveness for a listed drug, Accutane®, and the applicant conducted a Phase 3 trial in subjects 12 years of age and older (the relevant population for acne vulgaris and the population for whom the applicant seeks labeling), no additional pediatric trials are required. The Pediatric Research Equity Act (PREA) does not apply to this application because the proposed indication, active ingredient, dosage form, dosing regimen and route administration are the same as for the listed drug.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

Includes:

- Approved Proprietary name is Absorica™.
- Physician labeling has been discussed and resolved with the applicant. The Absorica™ approved physician labeling is in PLR format, while approved isotretinoin physician labeling is not required to be in PLR format. This difference should not lead to confusion regarding difference in safety profiles for these isotretinoin products. No differences in safety or efficacy profiles have been demonstrated between Absorica™ and approved isotretinoin. Any differences in the location or sequencing of information in the physician labeling occurs as a result of conversion of the label to the PLR format, and does not/should not imply differences in safety profile.
- Carton and immediate container labels have been discussed and resolved with the applicant.
- Patient labeling/Medication guide has been discussed and resolved with applicant

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This application will be approved.

- Risk Benefit Assessment – Cipher's application contains adequate information to demonstrate the safety and efficacy of Absorica™ for the treatment of nodular acne in patients 12 yrs and older. The application has provided adequate information in order to rely upon the Agency findings of safety and efficacy for isotretinoin. The risk and benefits of Absorica™ are similar to currently marketed isotretinoin products. Isotretinoin is an important therapeutic option for physicians and patients who manage acne vulgaris.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS) –

    - Because of the risk of teratogenicity and to minimize fetal exposure, isotretinoin is available only through a restricted program under a REMS called iPLEDGE. Under the isotretinoin REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program.
    - The REMS is necessary for Absorica™ capsules to ensure the benefits of the drug outweigh the risk of teratogenic effects associated with fetal exposure to tretinoin.

- The applicant provided the REMS, iPLEDGE, which is a single shared system for isotretinoin. The REMS consists of a Medication Guide, Elements to Assure Safe Use, Implementation System and Timetable for Submission of Assessments. In addition to the proposed REMS, the applicant submitted a "REMS supporting document": all relevant proposed REMS materials including: enrollment forms, informed consents, educational and communication materials.

- Recommendation for other Postmarketing Requirements and Commitments - The applicant has agreed to conduct an *in-vitro* dissolution method development study to define final test method parameters for quality control. Details of the study and the accompanying timeline have been agreed upon between the Agency and applicant.

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/s/

SUSAN J WALKER
05/25/2012