DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021951

NDA APPROVAL

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc, U.S. Agent
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) dated June 27, 2005, received July 1, 2005, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Absorica™ (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg, and 40 mg.

This new drug application provides for the use of Absorica™ (isotretinoin) Capsules for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

We acknowledge receipt of your amendments dated November 2, 3, and 17; December 23, 2005; February 1 and 9; April 18; May 8; October 26, 2006; March 9, 15, 22, and 30; May 1, 24, and 29; June 28; September 17; October 9; December 5, 2007; January 11; May 16, 2008; November 4, 2010; June 9 and 15; October 12 and 25; November 29; December 12 and 14, 2011; January 5; February 3, 15, 22, and 23; March 16, 20, 23, and 28; April 5, 12, 16, 18, 25, and 26; May 4, 17, and 25, 2012.

The November 29, 2011 submission constituted a complete response to our April 25, 2007 action letter.

The April 25, 2012 amendment contains a proposed risk evaluation and mitigation strategy (REMS) for Absorica™ (isotretinoin) Capsules.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021951**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1896-1 Conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for

your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

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

The timetable you submitted on May 4, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/12
Study/Trial Completion:	11/12
Final Report Submission:	11/12

Submit clinical protocols to your IND 064927 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Absorica™ (isotretinoin) Capsules to ensure the benefits of the drug outweigh the risk of teratogenicity. The details of the REMS requirements were outlined in our REMS notification letter dated April 12, 2012.

Pursuant to 505-1(f)(1), we have determined that Absorica™ (isotretinoin) Capsules can be approved only if elements necessary to assure safe use are required as part of a REMS to

mitigate the risk of teratogenicity that is listed in the labeling. The elements to assure safe use include:

- Healthcare providers who prescribe the drug are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- A centralized pregnancy registry for female patients who become pregnant and consent to participate in a root cause analysis

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. This single shared system, iPLEDGE, includes the following products:

NDA 021951 Absorica™ (isotretinoin) Capsules, 10, 20, 30, and 40 mg
ANDA 075945 Amnesteem® (isotretinoin) Capsules, 10, 20, and 40 mg
ANDA 076135 Clavaris™ (isotretinoin) Capusles, 20, 30, and 40 mg
ANDA 076356 Claravis™ (isotretinoin) Capsules, 10 mg
ANDA 076041 Sotret® (isotretinoin) Capsules, 10, 20, and 40 mg
ANDA 076503 Sotret® (isotretinoin) Capsules, 30 mg
ANDA 076485 Myorisan™ (isotretinoin) Capsules, 10, 20, and 40 mg

Other products may be added to the single shared system in the future if additional applications are approved.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on April 25, 2012, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Absorica™ (isotretinoin) Capsules into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following information:

1. Reports of operational audits, including results of distribution data reconciliation
2. Results of any prescriber, pharmacist, and patient surveys
3. An evaluation of patients' understanding of the serious risks of isotretinoin
4. A report on periodic assessments of dispensing of the Medication Guide in accordance with 21 CFR 208.24
5. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance

6. Non-Compliant Distribution 15-day Reports
7. Annual Internet Surveillance of isotretinoin Sales
8. Annual iPLEDGE Report with contents as described in the attachment to this letter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021951 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021951 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021951
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021951
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also remind you of your specific reporting obligations regarding serious adverse events in patients who have received Absorica™ (isotretinoin) Capsules. In addition to the usual

postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will submit a 15-day report for each of the following:

- All pregnancy exposures to Absorica™ (isotretinoin) Capsules; and
- All psychiatric events including suicides, attempted suicides, and suicidal ideation

In addition, you should continue to provide us with the following reports:

1. Annual Periodic Adverse Drug Experience Report
2. Special Pregnancy Periodic Biannual Report
3. Non-Compliant Distribution Reports
4. Psychiatric Quarterly Report

Any changes made to the iPLEDGE Non-Compliance Action Policy should be submitted with the iPLEDGE annual report.

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS and REMS appended materials
Annual iPLEDGE Report Contents

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

/s/

SUSAN J WALKER
05/25/2012