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APPLICATION NUMBER:
021951Orig1s000

OTHER ACTION LETTER(S)



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 October 26, 2006, received October 27, 2006, 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 October 26, 2006 and March 9 and 22, 2007.

The October 26, 2006 submission constituted a complete response to our May 1, 2006 action letter.

We also acknowledge receipt of your submissions dated March 15 and 30, 2007. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

Clinical

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

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

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

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

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

Chemistry, Manufacturing and Controls

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

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 a 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 Bauerlien, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Susan Walker, M.D.
Division 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/

Susan Walker

4/25/2007 02:43:55 PM



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-Isotreinoin.

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.



(b) (4)

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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  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:
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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
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/s/

Stanka Kukich
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