CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-025

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-025

Alba BioPharm Advisors, Inc.
Attention: Dr. William McCulloch
President/US Agent, TopoTarget A/S
12109 Betts Lane
Raleigh, NC 27614

Dear Dr. McCulloch:

Please refer to your new drug application (NDA) dated January 31, 2006, received February 1, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Totect™ 500 mg (dexrazoxane for injection).

We acknowledge receipt of your submissions dated March 16, March 17, March 29, and March 31; May 25 and May 31; June 5, June 9, and June 14; July 5, July 6, July 14, July 24(2), July 25; September 14, 2006, and November 22, 2006; January 24, March 19, March 21, March 22 and March 26, 2007; and May 18, 2007. The November 22, 2006 submission constituted a complete response to our August 1, 2006 action letter.

This new drug application provides for the use of Totect™ 500 mg (dexrazoxane for injection) for the treatment of extravasation resulting from IV anthracycline chemotherapy.

We completed our review of this application, as submitted and it is approvable.

Before the application can be approved; however, it will be necessary for you to address the following.

1. During a recent inspection of the Phama Hameln GMBH manufacturing facility for this application, our field investigator conveyed deficiencies to the facility representative. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. The final printed labeling (FPL) must be identical to the enclosed labeling text with the exception of the following changes to the immediate container and carton labels:

    a) The established name of the drug has been revised to "dexrazoxane" but the recommended statement "Each vial of dexrazoxane for injection contains 589 mg of dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane" is not captured on the side panels.

b) The storage statement does not include the temperature range allowed for excursion, i.e. 15-30°C. Therefore, the following statement should be included: "Excursions permitted between 15-30°C."

It will be necessary for you to submit draft/final labeling with the above revisions. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, submit proposed content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We remind you of your postmarketing study commitment in your submission dated March 9, 2007. This commitment is listed below.

You have agreed to complete and submit to the FDA the population pharmacokinetic analysis you have previously agreed to. This analysis will compare the population parameter estimates, including inter-individual variabilities, to the literature values for dexrazoxane. As is standard practice, the initial models should group all of the data for each patient (i.e., n = 6, not n = 18). Models incorporating inter-occasion variability should then be investigated. The relationship between dexrazoxane concentrations and clinical outcomes (extravasation-related and toxicity-related) should also be explored. The FDA will review these analyses and make a determination as to whether further pharmacokinetic data acquisition is needed. FDA has previously indicated that n=6 subjects (the current dataset) may be sufficient. If n=6 is not sufficient, n=15 subjects is very likely to be sufficient.

Protocol Submission:	03/29/2006
Study Start:	07/06/2006
Final Report Submission:	09/2007

Submit clinical protocols to your IND 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 this 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, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 the deficiency. 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 this division 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 Brenda Atkins, Regulatory Project Manager, at (301) 796-1324.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Justice
5/24/2007 11:38:41 AM

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Public Health Service
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Alba BioPharm Advisors, Inc.
Attention: Dr. William McCulloch
President/US Agent, TopoTarget A/S
12109 Betts Lane
Raleigh, NC 27614

Dear Dr. McCulloch:

Please refer to your new drug application (NDA) dated January 31, 2006, received February 1, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for dexrazoxane as hydrochloride for injection, 500 mg powder and solvent.

We acknowledge receipt of your submissions dated March 16, March 17, March 29, March 31, May 25, May 31, June 5, June 9, June 14, July 5, July 6, July 14, and July 24, 2006 (clinical), and to your July 19, 2006 electronic correspondence.

We also acknowledge receipt of your submissions dated July 24, 2006 (CMC microbiology), and July 25, 2006 (labeling). 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:

1. Our field investigator could not complete inspections of the drug product manufacturing facility at [redacted] because the facility was not ready for inspection. Your amendment dated March 31, 2006 states that [redacted] would not be ready for inspections until January 2007. Since this facility carries out testing of the [redacted] and since this function is critical to the assurance of product quality, the facility is required to be inspected before approval of the NDA. Therefore, in your resubmission, provide a statement of readiness of this facility for inspections. Satisfactory inspections are required before this application may be approved. b(4) b(4)

[redacted] b(4)

3. In your e-mail correspondence dated July 19, 2006, you proposed that the Agency accept a blanket assurance from you that all analytical methods are now USP compliant and that the corrected validation and related documents would be re-submitted post-approval. This approach is not acceptable. Provide a clear documentation of revised analytical methods and data on their validations in your resubmission.

4. Regarding the microbiological environmental monitoring program, provide the growth media, incubation conditions, and actions taken when alert and action levels are exceeded. Identify the air samplers used.

5. The product-specific bacterial filter retention study should be submitted as soon as it is complete along with the flow rate and pressure parameters used during production.

6. [redacted] has responded that they do not provide certification that their stoppers are free of endotoxins. Please provide validation data to demonstrate that the [redacted] stoppers are processed so that they are free of bacterial endotoxins. b(4)

7. The amended NDA response indicates that the production temperature set-point for the sterilization of the solvent is [redacted] However, the container-closure integrity test data provided are valid for a temperature set-point of [redacted] The inconsistencies regarding the temperature set-point of the sterilization cycle should be resolved with additional clarifications. b(4)

[redacted] b(4)

9. Regarding the pyroburden monitoring program of solvent vials, provide the sampling method along with SOP 1QW0061. Provide information on the % recovery of endotoxin and data on how much endotoxin is removed by the washing process.

The following are additional comments:

1. The floor plan diagrams should be updated to depict product flow to [redacted] lyophilizers instead of [redacted] (based on the sterilization validation data provided in the amendment, [redacted] lyophilizers are to be used for the product) and remove the [redacted] b(4)

   The updated floor plans should be available for inspection.

2. A meeting or conference call can be arranged to discuss the media fill acceptance criterion.

3. Regarding your comment on submitting updated SOPs and documents to the Agency, it is not necessary to submit the documents; however, they should be available for inspection.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file amendments, 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 this division 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 Brenda Atkins, Regulatory Project Manager, at (301) 796-1324.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
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/

Robert Justice
8/1/2006 12:00:37 PM