

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-025

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

1.3.5.2 Patent Certification

PARAGRAPH III CERTIFICATION**U.S. Patent No. 4,963,551**

United States Patent No. 4,963,551 is listed in FDA's publication APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (the "Orange Book") in connection with the Reference Listed Drug Zinecard® (dexrazoxane HCl). This 505(b)(2) NDA relies, in part, upon investigations conducted on Zinecard® to which the applicant (TopoTarget A/S) does not have a right of reference.

Pursuant to 21 U.S.C. § 355(b)(2)(A)(iii) and 21 C.F.R. §§ 314.50(i)(1)(i)(A)(3) and 314.54(a)(1)(vi), TopoTarget A/S hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,963,551 expires on December 21, 2007.

APPEARS THIS WAY ON ORIGINAL

METHOD OF USE STATEMENT
U.S. Patent No. 5,242,901

United States Patent No. 5,242,901 is listed in FDA's publication APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (the "Orange Book") in connection with the Reference Listed Drug Zinecard® (dexrazoxane HCl). This 505(b)(2) NDA relies, in part, upon investigations conducted on Zinecard® to which the applicant (TopoTarget A/S) does not have a right of reference.

U.S. Patent No. 5,242,901 is a method of use patent, and has been assigned the Orange Book "Use Code" U-339, indicating that the patent covers "PREVENTION OF CARDIO-TOXICITY CAUSED BY THE ADMINISTRATION OF DOXORUBICIN." This NDA seeks approval of dexrazoxane for the "treatment of anthracycline extravasation," and does not seek approval for prevention of cardiotoxicity caused by the administration of doxorubicin, or any other use approved for Zinecard.

Accordingly, pursuant to 21 U.S.C. § 355(b)(2)(B) and 21 C.F.R. §§ 314.50(i)(1)(iii)(A) and 314.54(a)(1)(vi), TopoTarget A/S hereby certifies pursuant to its opinion and to the best of its knowledge, that U.S. Patent No. 5,242,901 does not claim any of the proposed indications for the drug product that is the subject of this application.

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER
	NAME OF APPLICANT / NDA HOLDER TopoTarget A/S

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) Totect™	
ACTIVE INGREDIENT(S) dexrazoxane hydrochloride	STRENGTH(S) 500 mg
DOSAGE FORM Powder & solvent for Injection	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 6, 727, 253	b. Issue Date of Patent 04/27/2004	c. Expiration Date of Patent 03/13/2020
d. Name of Patent Owner TopoTarget A/S	Address (of Patent Owner) Symbion, Fruebjergvej 3	
	City/State 2100 Copenhagen, Denmark	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  William McCulloch, US Agent/President Alba BioPharm Advisors, Inc.	Address (of agent or representative named in 1.e.) 12109 Betts Lane	
	City/State Raleigh, NC	
	ZIP Code 27614	FAX Number (if available) (919) 848-6495
	Telephone Number (919) 848-6495	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
N/A

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 1-31 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.
Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Treatment of anthracycline extravasation during chemotherapy

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

25 JAN 06

PETER BULH JENSEN

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input checked="" type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name TopoTarget A/S	
Address Symbion Science Park Fruebjergvej 3	City/State 2100 Copenhagen, Denmark
ZIP Code	Telephone Number
FAX Number (if available)	E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-025

SUPPL #

HFD # 150

Trade Name Totect

Generic Name dexrazoxane for injection

Applicant Name TopoTarget A/S

Approval Date, If Known September 7, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-212

Zinecard

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

TT01 and TT02 - Two single-arm, open-label European studies comprise the clinical data.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TT01 and TT02 - Two single-arm, open-label European studies comprise the clinical data.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!

!

! NO

! Explain:

The two trials were European trials and were conducted prior to an IND # assignment.

Investigation #2

IND #

YES

!

!

! NO

! Explain:

The two trials were European trials and were conducted prior to an IND # assignment.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:
Study discussed at 11-9-04 industry
pre-IND meeting (minutes inserted in
Action Package).

Investigation #2 !
!
YES ! NO
Explain: ! Explain:
Study discussed at 11-9-04 industry
pre-IND meeting (minutes inserted in
Action Package).

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Brenda Atkins
Title: Regulatory Project Manager
Date: 9-5-07

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

APPEARS THIS WAY ON ORIGINAL

**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
9/6/2007 05:39:42 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 22-025 Resubmission Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 02-01-06 (original NDA)/11-24-06 NDA Resubmission PDUFA Goal Date: 05-24-07 NDA Resubmission

HFD 150 Trade and generic names/dosage form: Totect™ (dexrazoxane hydrochloride for injection)

Applicant: TopoTarget A/S Therapeutic Class: _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of extravasation resulting from IV anthracycline chemotherapy

this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-025

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

APPEARS THIS WAY ON ORIGINAL

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Brenda Atkins

5/21/2007 11:38:12 AM

1.3.3 Debarment Certification

TopoTarget A/S hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Annie Rasmussen
Chief Clinical Operations Officer
TopoTarget A/S

23/11 05

Date

APPEARS THIS WAY ON ORIGINAL

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-025	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Totect™ Established Name: dexarazoxane for injection Dosage Form: injection		Applicant: TopoTarget A/S
RPM: Brenda J. Atkins		Division: DDOP/HFD-150 Phone # 301.796.1324
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Zinecard (dexrazoxane for injection)/NDA 20-212 Provide a brief explanation of how this product is different from the listed drug. The two formulations of dexrazoxane are essentially identical. Both are lyophilized products of dexrazoxane containing only HCl as excipient but with slightly different pH values upon reconstitution due to process differences. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 5-21-07
❖ User Fee Goal Date ❖ Action Goal Date (if different)		May 24, 2007
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None Approvable letter issued 8-1-06 Approvable letter issued 5-24-07
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements:	
<input type="checkbox"/> Fast Track	
<input type="checkbox"/> Rolling Review	
<input type="checkbox"/> CMA Pilot 1	
<input type="checkbox"/> CMA Pilot 2	
<input checked="" type="checkbox"/> Orphan drug designation 3-25-04	
NDAs: Subpart H	BLAs: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)	<input type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)	<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart I	Subpart H
<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements:	
<input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• OC clearance for approval (<i>file communication in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst e-mail

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Robert Justice, M.D., Division Director – 7-31-06/Ann T. Farrell, M.D., Acting Deputy Director – 7-27-06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	5-24-07
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	6-18-07
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	1-10-06 (dated 1-10-06/rec'd 3-16-06)
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	6-18-07

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DMETS 5-16-07 & 8-30-07 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 5-16-06 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
-----------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	02-28-06
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	05-07-07
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	05-09-07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	8-1-06 (AE Letter) 5-24-07 (AE Letter)
❖ Internal memoranda, telecons, email, etc.	5-30-07
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	Pre-IND mtg 11-9-04
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	4-19-06/7-24-06/7-25-06/5-22-07/5-24-07/8-30-07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	

❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	4-5-07 and 7-13-06 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 8-29-07 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	7-26-06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested

Clinical Information

❖ Clinical review(s) (<i>indicate date for each review</i>)	7-20-06 & 5-7-07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See 7-20-06 Clinical review
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	See 7-20-06 Clinical review
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	See DSI's 7-18-06 review
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Joint review with Clinical review dated 7-20-06
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5-11-07

Atkins, Brenda J

From: Toyer, Denise P
Sent: Thursday, August 30, 2007 7:32 AM
To: Chan, Samuel; Park, Judy
Cc: Taylor, Kellie; Kim-Jung, Linda; Bridges, Todd; Holquist, Carol A; Atkins, Brenda J
Subject: RE: Request to Expedite DMETS review of Tradename for Totect

Brenda and Sam,

As noted the last review was completed on 5-23-07. Therefore, the 90 day clock expires effectively on 8-23-07. However, in light of the urgent nature of this request and the anticipated approval this week of this product we will expedite this request.

I've reviewed the products that have been approved by CDER from May 2007 through August 30, 2007 and have not identified any new names that have been recently approved that increase the potential for confusion with Totect. Therefore, this e-mail should serve as DMETS' review and that DMETS has no objection to the use of the proposed name Totect. Please note that I'm assuming that the approval of this NDA will occur prior to September 7, 2007. If the approval is delayed, please forward a consult to the OSE mailbox and we will expedite a more comprehensive 90 day review.

Sam, please capture this email as a final (aka preaction trademark) review and give it a AIMS number.

Please let me know if I can be of further assistance.

Denise

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
10903 New Hampshire Avenue,
CDER Building #22, Room 4414
Silver Spring, Maryland 20903
Phone: 301-796-0549 Fax: 301-796-9865

APPEARS THIS WAY ON ORIGINAL



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:

We acknowledge receipt on June 19, 2007 of your June 18, 2007 resubmission to your new drug application for Totect™ 500 mg (dexrazoxane for injection).

We consider this a complete, class 2 response to our May 24, 2007 action letter. Therefore, the user fee goal date is December 19, 2007.

If you have any question, call Brenda Atkins, Regulatory Project Manager, at (301) 796-1324.

Sincerely,

{See appended electronic signature page}

Brenda Atkins, B.S.
Regulatory Project Manager
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/

Brenda Atkins
7/12/2007 10:34:05 AM

MEMORANDUM OF TELECON

DATE: May 30, 2007

APPLICATION NUMBER: NDA 22-025, Totect (dexrazoxane) for injection

BETWEEN:

Name: Dr. William McCulloch, President, Alba BioPharm Advisors, Inc.

Phone: (919) 848 6495

Representing: US Agent for TopoTarget A/S

Others: TopoTarget A/S:

Peter Buhl Jensen, Chief Executive Officer, TopoTarget A/S
Elisabeth Vang Carstensen, Ph.D., Head of Drug Supply, QA
Anne Vinding Sillemann, MSc (Pharm), Head of Global Regulatory Affairs
Mads W. Jørgensen, MSc (Pharm), Regulatory Affairs Associate
Birte Odgaard Larsen, MSc (Pharm), International Regulatory Affairs
Manager/Project Manager for Totect

Regulus Pharmaceutical Consulting:

Kip Vought, Director, Regulatory Affairs
Nik Burlew, Director, Quality Assurance
Alyssa Carter, Manager, Regulatory Affairs

AND

Name: Brenda Atkins, Consumer Safety Officer, Division of Drug Oncology Products, CDER/OND; Ravi S. Harapanhalli, Ph.D., Branch Chief, Branch V (CMC-Pre-marketing), Division of Pre-marketing Assessment III and Manufacturing Science, Office of New Drug Quality Assessment (ONDQA); Sarah Pope, Ph.D., PAL/ONDQA;

SUBJECT: Sponsor's Request for FDA Guidance Regarding the Agency's May 24, 2007 NDA Approvable Action

The NDA was originally dated January 31, 2006, and resubmitted on November 22, 2006. The Agency's action on the NDA was an approvable (AE) action on May 24, 2007. The primary reason for the AE was because of cGMP deficiencies. The Agency's AE letter stated 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. “

On May 25, 2007 the corrective action proposed by the applicant stated “ _____”

b(4)

In this teleconference, the sponsor clarified that the Hameln site is an alternate manufacturing site for _____ The sponsor also confirmed that the Hameln site was not originally specified as an alternate (or secondary) _____ manufacturing site for the NDA. _____

b(4)

b(4)

FDA provided additional clarity to the sponsor on their proposal above. Dr. Harapanhalli first clarified that no final decisions could be made during the teleconference as the other FDA review disciplines involved would have to be included in any final decisions. In this particular situation, the Office of Compliance’s overall recommendation impacted the approvability of the NDA, and _____ from the NDA would not necessarily expedite an immediate approval action. In order to achieve an approval for the NDA, the Office of Compliance will need to issue an overall “acceptable” recommendation for all proposed manufacturing sites. _____

b(4)

b(4)

The following options were discussed:

b(4)

2. The applicant should provide comparative manufacturing descriptions for the Hameln site versus the Ben Venue site. The Agency pointed out that there were probably no CMC issues with the _____ involving both manufacturers, but that differences in performance of the _____, when mixed with the drug product, merit additional scientific evaluation.

b(4)

The Sponsor was instructed to officially submit a written proposal to their NDA, which, if deemed a complete response to the AE action, would be designated a “Major Amendment.” Even though a “Major Amendment” could receive a 6-month PDUFA clock, the Agency will do its best to expedite its review of it.

Sarah Pope, Ph.D.
Division of Pre-Marketing Assessment III
and Manufacturing Science
Branch V, PAL/Oncology
Office of New Drug Quality Assessment

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

/s/

Brenda Atkins
7/6/2007 03:40:40 PM
CSO

Sarah Pope
7/10/2007 09:32:44 AM
CHEMIST

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak BLDG 22, Room 4447
Center for Drug Evaluation and Research

TO: Robert Justice, MD
Director, Division of Drug Oncology Products, HFD-150

THROUGH: Kristina Arnwine, PharmD, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Judy Park, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

DATE: May 15, 2007

SUBJECT: DMETS Proprietary Name Review
Totect™
(Dexrazoxane for Injection)
500 mg/vial
NDA#: 22-025

OSE PROJECT #: 2007-1136

This memorandum pertains to a re-review of the proprietary name, Totect. DMETS and DDMAC found the proprietary name acceptable in our initial review (OSE consult #06-0109 dated July 18, 2006). DMETS also reviewed the container labels, carton and insert labeling in the aforementioned review. Subsequent to that review, revised labels and labeling were submitted and reviewed in OSE consult #2007-302 dated May 16, 2007.

Since our initial review, DMETS identified seven additional names with potential for confusion with Totect. They are Tritect, Tetrex, Duetact, Totelle Cycle™, Lotrel, Tolep (Italy), and Ketek. However, following analysis of these names, it was determined that DMETS will not further review the names due to the lack of significant look-alike and/or sound-alike similarities to Totect; in addition to differentiating product characteristics such as indication for use, product strength, usual dosage, route of administration, frequency of administration, dosage form, prescriber population, patient population, storage conditions, product unavailability, and/or area of marketing which minimize the potential for confusion. Thus, DMETS has no objection to the use of the proposed name Totect. Additionally, DDMAC finds the name, Totect, acceptable from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. Please copy DMETS on any correspondence to the sponsor on this issue. If you have any questions or need clarification, please contact Sam Chan, OSE Project Manager, at 301-796-2283.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public

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/s/

Judy Park
5/23/2007 09:34:05 AM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
5/23/2007 12:06:24 PM
DRUG SAFETY OFFICE REVIEWER
Acting Team Leader

Denise Toyer
5/23/2007 02:21:30 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/23/2007 02:35:52 PM
DRUG SAFETY OFFICE REVIEWER

FILE MEMORANDUM

TO: NDA 22-025

PM: BA

MEMO DATE: May 3, 2007

FROM: Robert Kane, MD, Medical Reviewer, Division of Drug Oncology Products

SUBJECT: Completion of labeling text with the NDA sponsor, TopoTarget

via: Ramzi Dagher, MD, team leader, DDOP, OODP

Background:

Totect™, Dexrazoxane for injection, received an approvable letter dated August 1, 2006, pending resolution of CMC and microbiology deficiencies. The combined clinical-statistical NDA review was entered into DFS on June 20, 2006. Following resolution of the deficiencies, labeling discussions with the sponsor have now been completed with agreement of the sponsor and FDA as of May 1, 2007. In the final labeling, changes in the clinical studies section were made to merge the findings of the two clinical studies as noted here.

CLINICAL STUDIES

Totect™ was studied in two open-label, single arm, multi-center studies testing whether Totect™ administration could reduce or avoid surgical intervention for tissue injury following anthracycline extravasation. In the two studies, eligible patients were receiving single-agent anthracycline intravenously (usually as part of combination chemotherapy) and developed extravasation symptoms of pain, burning, swelling, and/or redness near the infusion site. Skin biopsy samples from the suspected area were examined for the presence of anthracycline as determined by the presence of tissue fluorescence; however, therapy was not delayed for this test result.

In both studies, treatment with Totect™ was to begin as soon as possible and no later than 6 hours after extravasation with retreatment 24 and 48 hours later (a total of 3 doses). Totect™ was administered as 1-2 hour IV infusions through a different venous access location. The first and second doses were 1000 mg/m² and the third dose was 500 mg/m². No dose modifications were planned except for patients whose body surface area exceeded 2.0 m², in which case the total daily dose limit on the first and second day was 2000 mg/day and 1000 mg on the third day.

In total, 80 patients were enrolled and 54 were evaluable. Demographics in the two studies were similar. The median age was 57 years, and sixty-five percent of patients were women. The anthracyclines most commonly associated with extravasation were epirubicin (56%) and doxorubicin (41%). Peripheral IV sites of extravasation included the forearm in 63%, the hand in 21%, and the antecubital area in 11%; four patients (5%) received the anthracycline via a central venous access device (CVAD). Most patients

presented with swelling (83%), redness (78%), and pain (43%). In study 1, 11% also presented with blisters. The median baseline lesion area was 25 cm² (range 1-253 cm²).

Evaluable patients had to be receiving single-agent IV anthracycline at the time of extravasation, to have skin biopsies showing fluorescence, and to receive the first Totect™ dose within 6 hours of the extravasation.

In study 1, none of the 19 evaluable patients required surgical intervention and none had serious late sequelae. In study 2, one of the 38 evaluable patients required surgery. One additional non-evaluable patient required surgery for tissue necrosis. Thirteen patients had late sequelae at the event site such as site pain, fibrosis, atrophy, and local sensory disturbance; all were judged as mild except in the one patient who required surgery. None of the 4 patients with CVADs required surgical intervention.

No additional communication with the sponsor is required for this review.

APPEARS THIS WAY ON ORIGINAL

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/s/

Robert Kane
5/4/2007 12:50:56 PM
MEDICAL OFFICER

Ramzi Dagher
5/7/2007 10:34:48 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
22-025

APPLICANT INFORMATION

NAME OF APPLICANT TopoTarget A/S	DATE OF SUBMISSION 5/18/2007
TELEPHONE NO. (Include Area Code) 011 45 39 17 83 92	FACSIMILE (FAX) Number (Include Area Code) 011 45 39 17 94 92
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Symbion Science Park Fruebjergvej 3 DK-2100 Copenhagen Denmark	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Dr. William McCulloch Alba BioPharm Advisors, Inc. 12109 Betts Lane, Raleigh, NC 27614 Phone/fax 919-848-6495

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 22-025		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Dexrazoxane	PROPRIETARY NAME (trade name) IF ANY Totect™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Powder and Solvent for Injection	STRENGTHS: 500 mg	ROUTE OF ADMINISTRATION: Intravenous Administration
(PROPOSED) INDICATION(S) FOR USE: Treatment of anthracycline extravasation during chemotherapy		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Zinecard® (dexrazoxane for injection)</u> Holder of Approved Application <u>Pharmacia and Upjohn</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Written response to FDA request for fulfillment of post marketing commitment
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

- | | |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Index |
| <input type="checkbox"/> | 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) |
| <input type="checkbox"/> | 4. Chemistry section |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) Written response to FDA request for fulfillment of post marketing commitment |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:

Dr. Margaret McCulloch

5/18/07

ADDRESS (Street, City, State, and ZIP Code)

Alba BioPharm Advisors, Inc., 12109 Betts Lane, Raleigh, NC 27614

Telephone Number

(919) 848-6495

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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May 18th 2007

Dr. Robert Justice, MD
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products Document Room
5901-B Ammendale Rd
Beltsville, MD 20705-1266

**Subject: NDA 22-025
Totect™ 500mg Powder and Solvent for injection
Response to Request for fulfillment of a Post Marketing
Commitment – Study TT04 (FDA fax May 3rd 2007 and May
7th 2007)**

Dear Dr. Justice,

Pursuant to FDA faxes dated May 3rd and 7th regarding requests on fulfillment of a post marketing commitment, we are pleased to submit the attached signed letter from the sponsor, TopoTarget A/S, and request that this information be filed to NDA 22-025 for Totect™ 500mg Powder and Solvent for injection.

Please contact Dr. William McCulloch, US agent for TopoTarget A/S, at 919 848 6495 or bmcculloch@albaadvice.com if you require additional information or have questions about the submitted materials.

Yours sincerely,

Dr. W. McCulloch
Alba BioPharm Advisors Inc, US Agent for TopoTarget A/S

cc Brenda Atkins, project manager.

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22, Mail Stop 4447
Center for Drug Evaluation and Research**

TO: Robert Justice, MD
Director, Division of Drug Oncology Products, HFD-150

THROUGH: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Judy Park, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

DATE: March 7, 2007

SUBJECT: DMETS Labeling Review
Totect™
(Dexrazoxane for Injection)
500 mg/vial
NDA#: 22-025

OSE PROJECT #: 2007-302

This memorandum is in response to a request from the Division of Drug Oncology Products for a re-review of the labels and labeling for Totect submitted on January 24, 2007. DMETS and DDMAC found the proprietary name acceptable in our original review (OSE consult #06-0109 dated July 18, 2006). Label and labeling comments were also included in that review. However, the drug received an “approvable” action on August 1, 2006 and the labeling comments were not communicated to the sponsor. The sponsor submitted a complete response to the deficiency letter on November 24, 2006 and re-submitted the labels and labeling for review and comment. Additionally, the sponsor submitted samples of the proposed vials and caps for Totect. Since the container labels and carton labeling have not been revised from the previous submission, we are repeating our comments below for your convenience. In addition, we will review and comment on the revised Package Insert and the proposed vials and caps for Totect.

A. GENERAL COMMENT

1. We note the sponsor uses “dexrazoxane as hydrochloride” for the established name and “powder for injection” as the dosage form of this product. We recommend revising the established name to read as “dexrazoxane” because the strength is based on dexrazoxane and not the hydrochloride salt. The hydrochloride salt can be incorporated into the “Each vial contains...” statement as follows: “Each vial contains dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane” which can be presented on a side panel.
2. Additionally, powder is not a U.S.P. recognized, finished dosage form. The dosage form should be presented as “for Injection.” Therefore, revise the established name and dosage form to read as “dexrazoxane for injection” on all labels and labeling.

6 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

DMETS recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (The Project Manager Assigned to the LNC) and the assigned ONDQA Chemist regarding the proper designation of the the established name and dosage form.

B. TOTECT DRUG SUBSTANCE CONTAINER LABELS

1. Increase the prominence of the proprietary name because it appears small on the label.
2. The trademark symbol (™) is almost as prominent as the font size used for the proprietary name. Decrease the size of the trademark symbol so it is not confused as part of the proprietary name.
3. Delete the word “Powder” that appears in conjunction with the proprietary name. This is misleading as it appears that the proprietary name is “Totect Powder” rather than “Totect”. Additionally, the dosage form of this product is presented with the established name. See General Comment A.
4. The product strength is presented as “500 mg Powder for Injection”. Delete the phrase “Powder for Injection” as this is not representative of the strength. The strength should only be “500 mg/vial”.
5. Include the route of administration on the vial, if space permits. The statement should read as follows: “For Intravenous Use Only following reconstitution and dilution”.
6. Include the reconstitution instructions on the label, if space permits. Additionally, the following statement should be included, if space permits: “Once reconstituted with XX mL of XXX, the resultant solution contains XX mg/mL.”
7. DMETS is concerned with the colors of the current container labels. We recommend differentiating the container labels for the drug and diluent by presenting them in different colors.
8. Include a statement on the label that indicates that each vial is a single use vial and to discard the unused portions.
9. The unit for the storage temperature was omitted from the label as it currently reads: “Store below 25°”. Please revise the storage temperature to include the appropriate unit of measure (°C).
10. The following statement may be confusing: “Keep in the outer package in order to protect from light”. Revise this statement to read as follows in order to minimize confusion: “Protect from light. Keep vial in carton until ready for use”.
11. Decrease the prominence of the sponsors name (Topotarget) at the bottom of the container label. It appears almost as prominent as the proprietary name and may be misinterpreted as the proprietary name or even as the established name of the product.

C. DILUENT FOR RECONSTITUTION CONTAINER LABELS

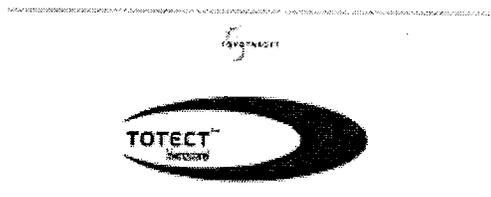
1. Replace the word “solvent” with “diluent” as this is a more accurate term.
2. Delete the proprietary name “Totect” from the vial label or at a minimum decrease the name in size. However, the drug name on the diluent vial may mislead the reader to believe that the vial actually contains the drug Totect, rather than diluent. We have seen such postmarketing errors despite the

phrase “This vial does not contain active drug”. It would be best to just include a statement that indicates the diluent is for reconstitution with only the drug product, Totect. The vial should be labeled as “Diluent for Totect Use Only.”

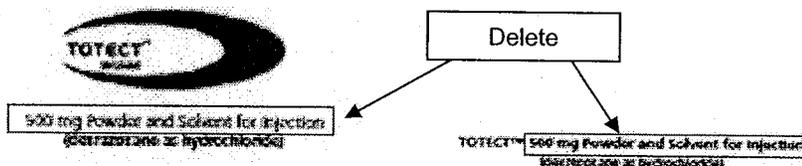
3. The vial labeled “Solvent” should indicate the name of the diluent and be labeled as “Sodium Lactate Injection, USP”.
4. Delete the statement “Solvent for Injection” as this may be mistakenly injected into a patient without reconstitution with drug product.
5. Differentiate the container labels for the drug and diluent by presenting them in different colors compared to one another.
6. See comments B9 through B11.

D. CARTON LABELING

1. See comment C1.
2. The Totect horseshoe-shaped logo is large and makes the drug name look like a company logo rather than a proprietary name. The logo should not interfere with, or be more prominent than the proprietary name. Thus, the sponsor should decrease the prominence or relocate the logo away from the proprietary name to avoid confusion. The established name and strength should be presented immediately following the proprietary name without intervening matter. Additionally, the size of the proprietary name and established name needs to be increased in size.



3. Delete the phrase “500 mg Powder and Solvent for Injection” that appears below the proprietary name on the main and side panels (see Figures. 1 and 2). The established name should appear underneath the proprietary name rather than this statement.



i. Fig. 1

Fig. 2

4. The current carton packaging of 10 vials each of the drug and the diluent is concerning. There is a strong likelihood that the drug vials will be separated from the diluent vials which can lead to errors. For example, a pharmacist may see the drug name on the carton, grab the diluent and mistaken it for the drug which can lead to administration of the diluent only. To avoid such errors, we recommend a physical linkage of the drug vial and the diluent vial. Examples include individually packaging one drug vial and one diluent vial together in a box or having a plastic ring to hold the two vials together.

These linked pairs can be packaged in a bigger carton of 10 vials of drug and diluent.

5. Revise the primary display panel to include an “Each carton contains” statement that describes the content of the carton. For example, revise the statement to read:

Each carton contains:
1 vial of Dexrazoxane for Injection 500 mg/vial
1 vial of XXXX (Diluent) (50mL)

6. Relocate the following statements to another panel in order to maximize space on the primary display panel for more pertinent information.

~~Powder for injection contains: 500 mg dexrazoxane as hydrochloride.~~
~~Solvent for injection contains: Sodium lactate 50% 1.87 g, Lactic acid q.s., Sodium hydroxide q.s., Water for injection q.s. ad 50 mL.~~

7. Revise the statement “For administration by i.v. infusion following mixing and dilution” to read “For Intravenous Use Only following reconstitution and dilution”. We do not recommend using the abbreviation “IV” on approved labels and labeling as the FDA launched a campaign in June 2006, warning health care providers and consumers not to use error-prone abbreviations. Thus, we request that the Office of New Drugs not approve or use abbreviations in their labels and labeling as they can be misinterpreted (e.g., the abbreviation “IV” which can be misinterpreted as the Roman numeral 4) and contribute to error.
8. Additionally, relocate the route of administration statement to the primary display panel as this information is important to the proper use of Totect. This statement should be prominent by bolding or some other means.

E. PACKAGE INSERT

1. See comments C1.
2. Replace the statement “Powder and Solvent for Injection” under Totect™ on top of page 1 with the established name “(dexrazoxane for injection)” (see General Comment A). Additionally, delete “Totect™ Package Insert” since it is redundant.
3. Dosage and Administration section
 - a. As currently presented the Dosage and Administration section is disorganized and confusing. For example, dosing information is contained in the directions for Mixing and Diluting subsection and the Administration subsection is entitled “Preparation and Administration” although no preparation instructions are included. Reorganize and rename the headings used in this section in the following sequential order so that it is easier for the reader to follow:
 - 1) Dosing
 - 2) Reconstitution and Dilution,
 - 3) Administration
 - 4) Handling and Disposal

Additionally, relocate the pertinent information to the appropriate sections.

- b. Dosing Subsection (currently entitled Dose)
- i. DMETS is unclear as to the difference in the recommended dose and the maximum recommended dose included in this section. When should practitioners use the recommended dose versus the maximum dose. Please clarify.
 - ii. As noted above in b(i) the recommended dose and the maximum dose are already included in this section. However, the second paragraph in the current *Directions for Mixing and Diluting* subsection states “The individual dosage is based on calculation of the body surface area (BSA) up to a maximum dose of 2000 mg (each on day 1 and 2) and 1000 mg (day 3), corresponding to a BSA of 2 m². DMETS is unclear as to the meaning of BSA of 2 m². If the dose should be calculated on the BSA and practitioners should not use the information provided in b(i), then a specific milligrams per BSA should be provided.
- c. Reconstitution and Dilution Subsection (currently entitled Preparation of the Totect mixed and diluted solution)
- i. See Comments C1 and C2.
 - ii. Include the final concentration of the reconstituted solution (i.e. 10 mg/mL dexrazoxane HCl). Use the following type of statement: After reconstitution of Totect for Injection with 50 mL “Name of Diluent” the final concentration is XX mg/mL.
 - iii. The terms used throughout the labeling are inconsistent and may lead to confusion because they are not terms commonly used by healthcare providers. Thus, we recommend revising the terms as follows.
 - (a) Replace the words “mixing” and “diluting” with “reconstitution” and “dilution”, respectively, throughout this section.
 - (b) Currently, terms such as “mixed solution,” “solution,” and reconstituted product are used interchangeably. Maintain consistency in terminology referring to the reconstituted solution (drug and diluent). We recommend using the terminology “reconstituted solution” to maintain consistency in terminology.
 - iv. Revise step 3 to “Inject the calculated volume of reconstituted Totect into the infusion bag of 1000 mL of 0.9% NaCl. The Totect solution must not be mixed with any other drugs.”
 - v. The current Step 4 is confusing. Most hospital pharmacists will reconstitute all the vials needed then add the final volume to the infusion bag. Please clarify if this is permitted and if so, revise the steps accordingly.
 - vi. Clarify the statement “The product is stable for 4 hours from the time of mixing and diluting when stored **below** 25°C (77°F)”. Clarify if the reconstituted solution is stable at room temperature for 4 hours or must be refrigerated. Additionally, clarify if the storage requirement refers to the reconstituted solution or diluted solution.
 - vii. Clarify if Totect needs to be “protected from light” once it is reconstituted. The current statement “infused...under...*normal light conditions*.” is confusing and doesn’t communicate if the product needs to be protected from light. If Totect (after dilution) should be protected

from light, revise the statement “normal light conditions” to correctly reflect the light requirement.

d. Administration Subsection (currently entitled Preparation and Administration)

- i. Delete references to Preparation since hospital pharmacists will likely prepare the drug for administration by others and this information is included in another section.
- ii. Specify the usage time requirement (e.g. within XX minutes or hours) instead of the statement “immediately after preparation.” Additionally, this statement contradicts the 4 hour stability time presented in the Reconstitution and Dilution subsection.

e. Handling and Disposal Subsection (Currently entitled Instructions for Handling, and disposal)

DMETS is unclear what the sponsor is trying to communicate with the statement “There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.” Please explain the meaning of this statement as it appears cautionary in nature but does not clearly explain what the caution is.

4. How Supplied section

- a. Relocate the third sentence under the current *Direction for Mixing and Diluting* section to this section as this is the more appropriate section (i.e., Totect is provided in an individual patient treatment kit containing 10 vials of Totect.... treatment for 1 patient.)

5. Storage section

- a. See comments E.3(c)(vi) and E.3(c)(vii).

F. TOTECT VIALS/CAPS

- 1. The sponsor requested a review of the vial cap colors of Totect on November 24, 2006. DMETS compared the proposed vial caps and container labels of Totect to other marketed dexarazoxane products such as Zinecard[®] and generic dexarazoxane by Bedford Laboratories. Both the Zinecard and generic dexarazoxane are available in 250 mg and 500 mg strengths and the strengths are differentiated by a different vial cap color. Within each product strength, the same cap color is used for both the drug and its diluent. See Tables 1 and 2 below.

Table 1:

	Zinecard 250 mg		Zinecard 500 mg	
	Drug	Diluent	Drug	Diluent
Cap Color	Red	Red	Blue	Blue
Primary Container Label Color	Pink	Red	Aqua	Light Blue

Table 2:

	Generic Dexarazoxane 250 mg		Generic Dexarazoxane 500 mg	
	Drug	Diluent	Drug	Diluent
Cap Color	Grey	Grey	Aqua	Aqua
Primary Container Label Color	Grey	Black	Aqua	Red

The differentiating factor is the different colors used on the primary container labels for the drug and diluent. DMETS has no objections to the proposed vial cap colors of Totect (red) and diluent (white). However, DMETS is concerned with the colors of the current container labels. We recommend differentiating the container labels for the drug and diluent by presenting them in different colors. See comments B-7 and C-5.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sam Chan, OSE Project Manager, at 301-796-2283.

6 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
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/s/

Judy Park
5/15/2007 05:00:53 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/16/2007 10:48:12 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/16/2007 10:57:48 AM
DRUG SAFETY OFFICE REVIEWER

May 9, 2007

Dr. Robert Justice, MD
 Director
 Food and Drug Administration
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 Division of Drug Oncology Products Document Room
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 CVR-nr: 25695771

www.topotarget.com

Subject: NDA 22-025
Totect™ 500 mg Powder and Solvent for injection
Response to Request for fulfillment of a Post Marketing
Commitment – Study TT04 (FDA fax May 3th, 2007 and
May 7th, 2007)

Dear Dr. Justice,

Referring to faxes from FDA dated May 3rd, 2007 and May 7th 2007, TopoTarget A/S is hereby providing FDA with a response to the post marketing commitment request.

Description of commitment: TopoTarget A/S commits to complete and submit to FDA the population pharmacokinetic analysis you have previously requested. 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 will group all of the data for each patient (i.e., n=6, not n=18). Models incorporating inter-occasion variability will then be investigated. The relationship between dexrazoxane concentrations and clinical outcomes (extravasation-related and toxicity-related) will also be explored. As you informed us, 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 (the current dataset) may be sufficient. If n=6 is not sufficient, n=15 subjects is very likely to be sufficient.

Protocol submission: The protocol has already been submitted

Study Start: The study has already been started

Final Report submission: TopoTarget A/S anticipates providing FDA with a final TT04 Study Report based on 6 patients in September 2007

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FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 3 **Date:** May 7, 2007

Re: NDA 22-025 – Totect™ (dexrazoxane as hydrochloride) – Revised Request for Fulfillment of a Post Marketing Commitment

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Dear Dr. McCullough:

To clarify the Division's May 3, 2007 fax requesting that TopoTarget A/S commit to fulfill a Post Marketing Commitment, we are providing a more detailed description of that commitment. Please provide a proposed date of fulfillment (see underline below) to the Agency with a **FINAL REPORT SUBMISSION** (see **bolded** text below) no later than May 10, 2007 (both by email and officially to your NDA).

Description of Commitment: TopoTarget A/S commits 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. We 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: not applicable, the protocol has already been submitted

Study Start: not applicable, the study has already been started

Final Report Submission: _____

Please provide your commitment in writing by fax as soon as possible and formally to the NDA. We will need your response before an action is taken on your NDA. Please contact me if you have any questions. Thanks.

Sincerely,

Brenda Atkins, Regulatory Project Manager

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

/s/

Brenda Atkins
5/7/2007 11:43:12 AM
CSO

Atkins, Brenda J

From: Atkins, Brenda J
Sent: Wednesday, July 19, 2006 4:16 PM
To: 'William McCulloch'
Subject: RE: Amendment to NDA #22-025 and Questions

Dear Bill:

Our responses to your questions follow.

Question #1

Yes. Please submit a formal submission to the NDA addressed to Dr. Justice regarding readiness for inspection by ICS.

Question #2

No. We cannot accept a blanket statement as described under this question. An amendment to reflect the change in the methods and data on the limited validation should be submitted to the NDA.

Sincerely,

Brenda

From: William McCulloch [<mailto:bmcculloch@albaadvice.com>]
Sent: Wednesday, July 19, 2006 8:45 AM
To: Atkins, Brenda J
Subject: Amendment to NDA #22-025 and Questions

Dear Brenda:

With this e-mail I am sending a copy of an Amendment which will arrive in the document room today. Given the short time frame to the PDUFA date, I was worried that the Amendment might not reach you until next week by the usual channels.

There are two other questions outstanding which I believe might affect the NDA:

1. ICS in Kentucky has told us they are now ready for inspection. They apparently informed the local FDA office in KY of this last week but my question is whether you want some kind of formal submission to the NDA through you/Dr. Justice to record this availability?
2. There had been a question in some of the chemistry documents of validation methods not using USP. These have all been corrected now and all methods have been changed to refer to current USP. However, since the changes are merely in validation methods and are not substantive, it would seem cumbersome to re-submit all the documents at this stage since I am sure the reviewers will not be able to look at them even if we can get them into their hands in time. Would you accept some kind of blanket assurance that all methods are now USP and then we could re-submit the corrected documents after August 1?

<< File: 20060718 Amendment 14 final.pdf >>
Best regards,

Bill

Dr. W. McCulloch
President
Alba BioPharm Advisors, Inc.,
12109 Betts Lane,

Raleigh NC 27614
(919) 848 6495 Phone and Fax
(919) 201 6699 Mobile
www.albaadvice.com

APPEARS THIS WAY ON ORIGINAL

Atkins, Brenda J

From: Harapanhalli, Ravi S
Sent: Wednesday, July 19, 2006 3:44 PM
To: Atkins, Brenda J; Epps, Leon; Pope, Sarah
Cc: Kane, Robert; Farrell, Ann T; Dagher, Ramzi; Harapanhalli, Ravi S
Subject: RE: Amendment to NDA #22-025 and Questions

Response to Q 1: Yes, they should submit a documentation to the NDA regarding readiness for inspection by ICS.
Response to Q 2: No, we cannot accept blanket statement like this. An amendment to reflect the change in the methods and data on their limited validation should be submitted to the NDA.

Thanks

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Atkins, Brenda J
Sent: Wednesday, July 19, 2006 3:28 PM
To: Epps, Leon; Harapanhalli, Ravi S; Pope, Sarah
Cc: Kane, Robert; Farrell, Ann T; Dagher, Ramzi
Subject: FW: Amendment to NDA #22-025 and Questions

FYI

From: William McCulloch [<mailto:bmcculloch@albaadvice.com>]
Sent: Wednesday, July 19, 2006 8:45 AM
To: Atkins, Brenda J
Subject: Amendment to NDA #22-025 and Questions

Dear Brenda:

With this e-mail I am sending a copy of an Amendment which will arrive in the document room today. Given the short time frame to the PDUFA date, I was worried that the Amendment might not reach you until next week by the usual channels.

There are two other questions outstanding which I believe might affect the NDA:

1. ICS in Kentucky has told us they are now ready for inspection. They apparently informed the local FDA office in KY of this last week but my question is whether you want some kind of formal submission to the NDA through you/Dr. Justice to record this availability?
2. There had been a question in some of the chemistry documents of validation methods not using USP. These have all been corrected now and all methods have been changed to refer to current USP. However, since the changes are merely in validation methods and are not substantive, it would seem cumbersome to re-submit all the documents at this stage since I am sure the reviewers will not be able to look at them even if we can get them into their hands in time. Would you accept some kind of blanket assurance that all methods are now USP and then we could re-submit the corrected documents after August 1?

<< File: 20060718 Amendment 14 final.pdf >>
Best regards,

Bill

Dr. W. McCulloch
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Raleigh NC 27614
(919) 848 6495 Phone and Fax
(919) 201 6699 Mobile
www.albaadvice.com

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

TopoTarget A/S

DATE OF SUBMISSION

7/18/06

TELEPHONE NO. (Include Area Code)

011 45 3917 83 92

FACSIMILE (FAX) Number (Include Area Code)

011 45 3917 94 92

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Symbion Science Park
Fruebjergvej 3
DK-2100 Copenhagen
Denmark

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Dr. William McCulloch
Alba BioPharm Advisors, Inc.
12109 Betts Lane, Raleigh, NC 27614
Phone/fax 919-848-6495

RECEIVED

JUL 20 2006

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 22-025

CDER White Oak DR

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Dexrazoxane

PROPRIETARY NAME (trade name) IF ANY

Totect™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM:

Powder and Solvent for Injection

STRENGTHS:

500 mg

ROUTE OF ADMINISTRATION:

Intravenous Administration

(PROPOSED) INDICATION(S) FOR USE:

Treatment of anthracycline extravasation during chemotherapy

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

- 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Zinecard® (dexrazoxane for injection)

Holder of Approved Application Pharmacia and Upjohn

TYPE OF SUBMISSION (check one)

- ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

- CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Documentation for notification of Paragraph IV certification.

PROPOSED MARKETING STATUS (check one)

- PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment 1

CDER/CDR

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment 2

RECEIVED

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Alyssa Carter for Bill McCulloch</i>	TYPED NAME AND TITLE Dr. William McCulloch	DATE: 07/18/06
---------------------------------------------------------------------------------------	-----------------------------------------------	-------------------

ADDRESS (Street, City, State, and ZIP Code) Alba BioPharm Advisors, Inc., 12109 Betts Lane, Raleigh, NC 27614	Telephone Number (919) 848-6495
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Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448
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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: July 17, 2006

TO: Brenda Atkins, Regulatory Project Manager
Robert Kane, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of all EIRs

NDA: 22025/000

NME: Yes

APPLICANT: TopoTarget A/S

DRUG: Totect™ (dexrazoxane) Injection

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of anthracycline extravasation during chemotherapy

CONSULTATION REQUEST DATE: April 5, 2006

DIVISION ACTION GOAL DATE: August 1, 2006

PDUFA DATE: August 1, 2006

I. BACKGROUND:

Drug Product:

Totect™ (dexrazoxane as a hydrochloride) is a formulation intended for use in the treatment of extravasation occurring during anthracycline chemotherapy. Accidental extravasation of anthracyclines (such as doxorubicin and epirubicin) is an unintentional paravenous infusion of tissues. Such events may cause severe, progressive tissue necrosis that can appear within hours or days of anthracycline use. Tissue damage can progress leading to severe pain, risk of infection, joint destruction, lesion of nerves and permanent dysfunction and cosmetic changes to

the effected tissues. Surgical removal of any damaged tissue with subsequent skin grafting is typically required. In addition, chemotherapy dose and regimen and schedules are often delayed due to these serious adverse events. Dexrazoxane readily enters cells and is hydrolyzed to form a chelating agent similar to EDTA. It catalytically inhibits topoisomerase II and can be a potent chelator of heavy metals, such as iron. It is not known to what extent these mechanisms of action contribute to the protective effect in anthracycline extravasation. This product is a new molecular entity and has been given orphan drug status.

The sponsor seeks approval for the use of dexrazoxane (Totect™) for the treatment of acute (< 6 hour after onset) anthracycline extravasation during chemotherapy. Patients receiving anthracycline-based chemotherapy may be identified as having acute drug extravasation, and may be enrolled into the study immediately and prior to consult with a surgeon, based on clinical assessment and either/or pain, swelling or redness at the site. A positive local biopsy for the drug substance, anthracycline-based agents, is required for confirmation of the diagnosis of anthracycline extravasation for the purposes of this study. Those enrolled subjects who did not have a confirmed diagnosis according to the protocol guidelines were assessed for safety but not efficacy.

The 4 clinical investigators selected for audit participated as primary investigators on the protocol, TT01. Their corresponding study centers represent 4 of 10 study sites, all of which were within Denmark. The study was open-labeled, single-arm, phase II, multicenter with an originally planned enrollment target of 25 subjects. Twenty three subjects were randomized into the study, of which 18 were evaluable for efficacy. Twelve subjects were randomized at the 4 sites identified for inspection.

II. RESULTS:

Inspected Entity	City, State/Country	Protocol(s)	Inspection Dates	EIR Received Date	Final Classification
Professor Henning Mouridsen	Copenhagen, Denmark	TT01	June 2006	Pending DAL-DO	Pending
Niels Borregaard	Copenhagen, Denmark	TT01	June 2006	Pending DAL-DO	Pending
Torben Skovsgaard	Herlev, Denmark	TT01	June 2006	Pending DAL-DO	Pending
Bjarne A. Jensen	Herlev, Denmark	TT01	June 2006	Pending DAL-DO	Pending

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

1. Professor Henning Mouridsen
Rigshospitalet
The Finsen Centre
Department of Oncology
Blegdamsvej 9
DK-2100 Copenhagen, Denmark

- a. **What was inspected?**

The study records of 5 of the 5 subjects enrolled into the study, and under the responsible care of Professor Mouridsen, were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 5 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects.

- b. **Limitations of inspection:** The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Danish. Field investigator Mr. Patrick Stone had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Mr. Stone accept the interpretation support and products provided in support of the CI inspection and the outcome.

- c. **General observations/commentary:**

The site was found to be adequate in the execution of the study TT01. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Source data were audited for 5 subjects. IRB/EC compliance was verified and test article accountability records were found to be sufficient. All AEs were reported and followed up.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on communication from the field investigator, Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- d. **Assessment of data integrity:** The data from Henning Mouridsen's site, associated with protocol TT01, submitted to the agency in support of NDA 22025, are reliable.

2. Consultant Niels Borregaard
Rigshospitalet
The Finsen Centre
Department of Hematology
Blegdamsvej 9
DK-2100 Copenhagen, Denmark

- a. **What was inspected?**

The study records of 3 of the 3 subjects enrolled into the study, and under the responsible care of Niels Borregaard, were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 3 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs

in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Danish. Field investigator Mr. Patrick Stone had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Mr. Stone accept the interpretation support and products provided in support of the CI inspection and the outcome.

c. General observations/commentary

The site was found to be adequate in the execution of the study TT01. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Source data were audited for 3 subjects. IRB/EC compliance was verified and test article accountability records were found to be sufficient. All AEs were reported and followed up.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on communication from the field investigator, Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Niels Borregaard's site, associated with Protocol TT01, submitted to the agency in support of NDA 22025, are reliable.

3. Consultant Torben Skovsgaard
Herlev County Hospital
Department of Oncology
Herlev Ringvej 75
DK-2730 Herlev, Denmark

a. What was inspected? The study records of 1 subject enrolled into the study, and under the responsible care of Torben Skovsgaard, was audited in accordance with the clinical investigator compliance program, CP 7348.811. For this 1 subject the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death if applicable and informed consent forms for the subject.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Danish. Field investigator Mr. Patrick Stone had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Mr. Stone accept the interpretation support and products provided in support of the CI inspection and the outcome.

c. General observations/commentary:

The site was found to be adequate in the execution of the study TT01. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Source data were audited for the subject. IRB/EC

compliance was verified and test article accountability records were found to be sufficient. Applicable AEs were reported and followed up.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on communication from the field investigator, Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Torben Skovsgaard's site, associated with Protocol TT01, submitted to the agency in support of NDA 22025, are reliable.

4. Consultant Bjarne A. Jensen
Herlev County Hospital
Department of Hematology
Herlev Ringvej 75
DK-2730 Herlev, Denmark

a. What was inspected? The study records of 3 of the 3 subjects enrolled into the study, and under the responsible care of Bjarne Jensen, were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 3 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Danish. Field investigator Mr. Patrick Stone had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Mr. Stone accept the interpretation support and products provided in support of the CI inspection and the outcome.

c. General observations/commentary:

The site was found to be adequate in the execution of the study TT01. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Source data were audited for 3 subjects. IRB/EC compliance was verified and test article accountability records were found to be sufficient. All AEs were reported and followed up.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on communication from the field investigator, Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Bjarne Jensen's site, associated with Protocol TT01, submitted to the agency in support of NDA 22025, are reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study data collected by Professor Henning Mouridsen, Consultant Niels Borregaard, Consultant Torben Skovsgaard and Consultant Bjarne A. Jensen appear reliable.

The FDA investigator, Mr. Patrick Stone reported in preliminary communications to DSI that he inspected 1 subject under the responsible care of Torben Skovsgaard, 3 subjects under the care of Bjarne A. Jensen, 5 subjects under the care of Henning Mouridsen, and 3 subjects under the care of Niels Borregaard. 100% of the CRFs and corresponding source documents were reconciled for each subject audited. Adverse events were recorded and reported in accordance with the protocol and no serious adverse events were observed. No notable objectionable observations were made. An FDA Form 483 was not issued to any of the 4 clinical investigators. It was noted that for each site there were numerous study sub-investigators. It appeared that none of the primary clinical investigators directly attended to the patients. Notwithstanding this observation all 4 sites well executed and managed the study TT01.

Observations noted above are based on the preliminary communications provided the field investigator Mr. Patrick Stone. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

APPEARS THIS WAY ON ORIGINAL

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

/s/

Lauren Iacono-Connors
7/17/2006 05:30:07 PM
UNKNOWN

Leslie Ball
7/18/2006 09:08:28 PM
MEDICAL OFFICER

Our response to your questions follows:

"The LOA to reference the DMF should be included in the comparability protocol and should be submitted for review within this review period in order for you to effect changes following approval of the NDA. Note that the comparability protocol should have been reviewed and approved by the Agency in conjunction with the CMC review of the NDA for you to make proposed change. Alternatively, if you cannot submit the requested information, you may submit a comparability protocol in the form of a separate prior-approval supplement after the NDA is approved. In that case, you cannot make the proposed change until the protocol has been reviewed and approved."

Please call at 301-796-1324 if further discussions are needed.

Brenda

APPEARS THIS WAY ON ORIGINAL

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

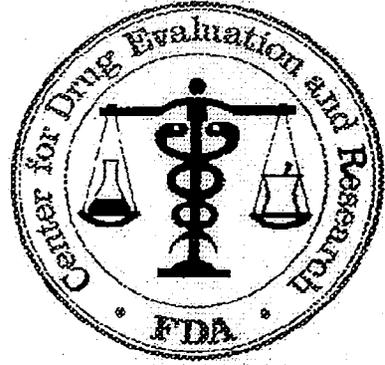
/s/

Brenda Atkins

6/29/2006 04:54:37 PM

CSO

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** June 29, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane) - Chemistry Information Requests

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Regarding your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006. In response to your June 28, 2006 e-mail stating the following:

“Pursuant to our conversation, the point upon which we need clarification is whether FDA wants us to reference _____ Ben Venue Labs facilities (Type I) DMF _____, or if they expect _____ to file a new (Type II) DMF for the _____. Unfortunately, if it is the latter, we cannot do this within the next week and so cannot file the comparability protocol in the timelines discussed with the FDA chemistry reviewers.”

b(4)

In response to the above issues we request the following:

A Type II DMF or adequate information on the manufacture and controls as an amendment to the NDA is needed.

Please call at 301-796-1324 if further discussions are needed.

Brenda

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/s/

Brenda Atkins
6/29/2006 12:14:57 PM
CSO

Atkins, Brenda J

From: Lolos, Anastasia
ent: Thursday, June 22, 2006 11:21 AM
o: Atkins, Brenda J
Subject: RE: NDA 22-025 Totect

Brenda,

I just got a response from the DMF holder regarding a deficiency letter that I had sent to them about the stoppers used for Totect. So I need to send one additional question to the firm. Since they have not submitted the amendment yet, they can add this question to the rest and submit it all together.

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

Thanks, Brenda.

Anastasia

From: Atkins, Brenda J
Sent: Thursday, June 22, 2006 10:07 AM
To: Lolos, Anastasia
Subject: RE: NDA 22-025 Totect

Anastasia:

I'm afraid not. I will call the sponsor today for a status update re. your requests.

Brenda

From: Lolos, Anastasia
Sent: Thursday, June 22, 2006 9:50 AM
To: Atkins, Brenda J
Subject: NDA 22-025 Totect

Brenda,

I saw in the system that the firm submitted recently 2 BC and 1 BZ amendment. Do you know if any of these contained the responses to my information request?

Thank you.

Anastasia G. Lolos
Reviewer, New Drug Microbiology Staff
OPS/CDER
301-796-1566

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** June 22, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane) – Microbiology Request

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Please refer to your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006.

Here is an additional request to be added to our requests listed in the May 11, 2006 fax.

Regarding the stoppers used for Totect™, _____ responded that they do not provide certification that their stoppers are free of endotoxins. Please provide validation data to demonstrate that the _____ stoppers are processed so that they are free of bacterial endotoxins.

b(4)

Your response to the above request should be submitted officially to your NDA 22-025. Please call at 301-796-1324 if further discussions are needed.

Sincerely,

Brenda

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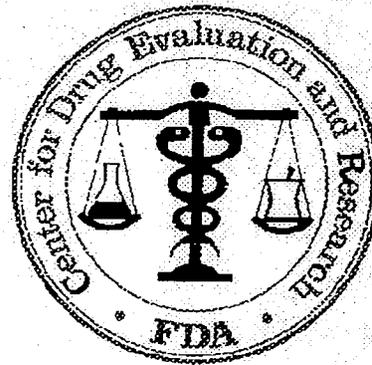
/s/

Brenda Atkins
6/22/2006 04:15:07 PM
CSO

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** June 9, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane) - Chemistry Information Requests

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Regarding your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006, please respond to the following requests **as soon as possible**.

1. Stability updates for the reconstitution solvent should be submitted for review as soon as possible.
2. Please confirm the site responsibilities and inspection readiness status for the Integrated Commercialization (Brooks, Kentucky) site.

In addition the chemistry review team of your NDA requests a brief teleconference (30 minutes) with you for further discussions. I will be contacting you later today with possible teleconference dates.

Please call at 301-796-1324 if further discussions are needed.

b(4)

b(4)

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/s/

Brenda Atkins

6/9/2006 07:37:37 AM

CSO

Atkins, Brenda J

From: Pope, Sarah
Sent: Thursday, June 08, 2006 4:04 PM
To: Atkins, Brenda J
Cc: Epps, Leon; Harapanhalli, Ravi S
Subject: CMC comments for NDA 22-025

Importance: High

Hi Brenda,

Please convey the following two comments to the firm asap. Please note Leon's review is still ongoing, and that further comments may be issued.

1. Stability updates for the reconstitution solvent should be submitted for review as soon as possible.
2. Please confirm the site responsibilities and inspection readiness status for the Integrated Commercialization (Brooks, Kentucky) site.

Please schedule a short (30-min) teleconference with the firm as a follow-up to this request. Ravi, Leon, and I should be invited.

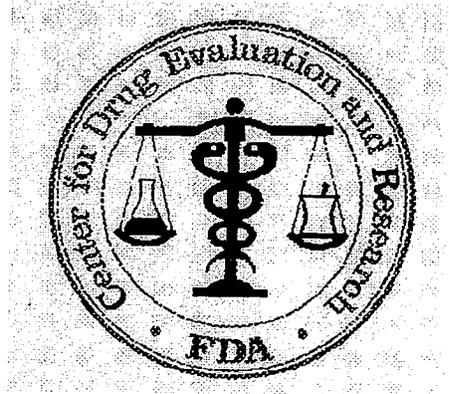
Thanks,
Sarah

APPEARS THIS WAY ON ORIGINAL

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 4 **Date:** May 11, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane) – Microbiology Requests

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Please refer to your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006.

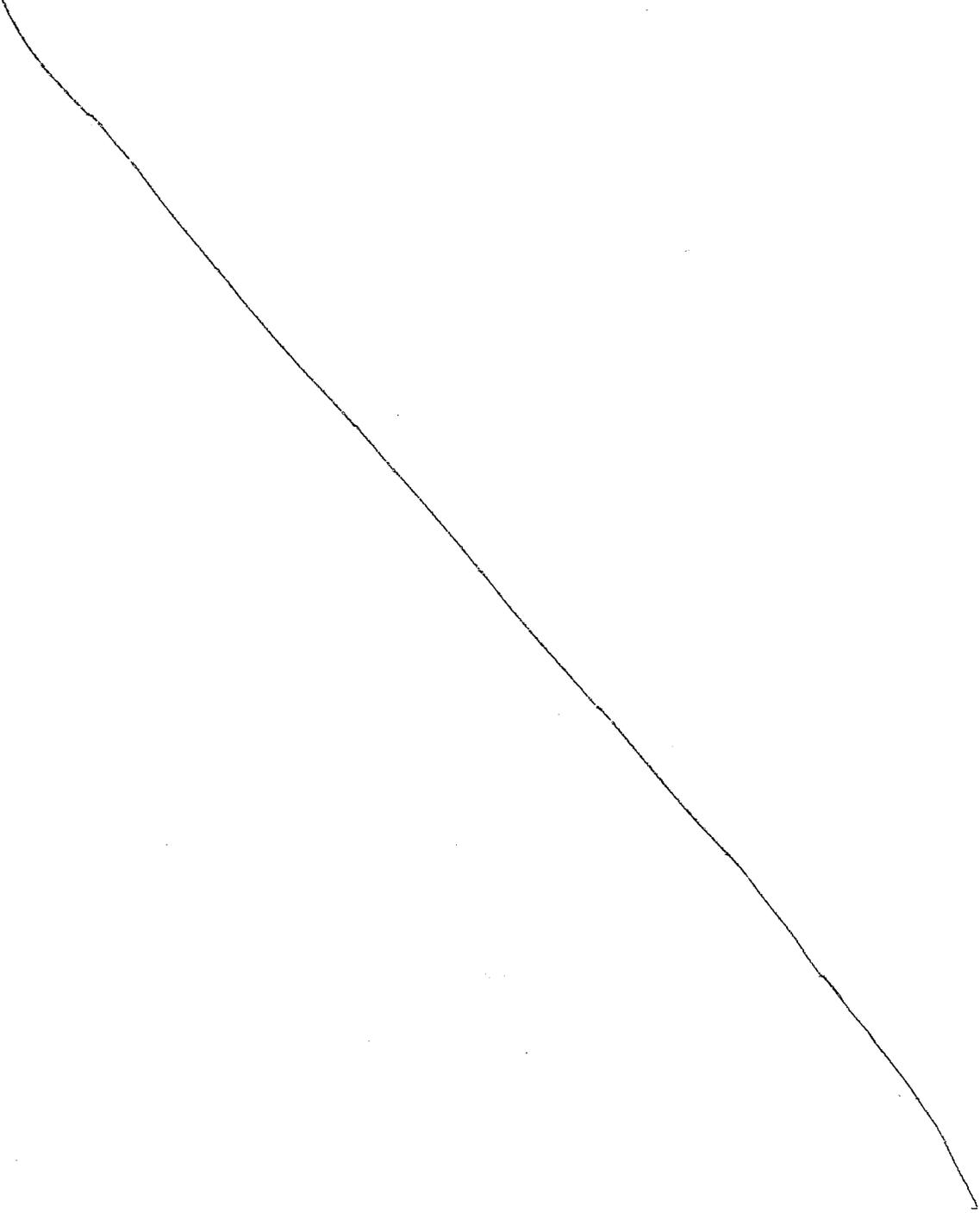
We strongly advise that you review the November 1994 FDA *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

Please provide the following:

Lyophilized powder

1. A floor plan of the ~~_____~~ filling facilities, the location of all critical equipment, material, personnel and product flow. b(4)
2. Filter retention validation data for the sterilizing filters. In addition, the ~~_____~~ filters should be described (type, manufacturer) in more detail. The water and product bubble points, the maximum flow rate and pressure that will be used during manufacture should be submitted. b(4)
3. The holding time between start of compounding and start of filling as well as the holding times for sterilized materials. Please provide a statement stating if the critical operations and holding times have been validated though media fill runs.

6-22-06 requests
status
update



b(4)

b(4)

b(4)

b(4)

Solvent

1. Information regarding the _____ of the vials used in the manufacture of the drug product.

b(4)

2. _____

b(4)

3. The methods and controls to monitor the routine production cycles as well as the acceptance criteria for these.
4. A description of the program for routine and unscheduled requalification of production _____ and reprocessing (if any). **b(4)**
5. Media and incubation conditions for all types of environmental monitoring.
6. Validation data for the _____ sterilization of the solvent. It is not clear what process was validated with the study included in this application. Did the study validate the minimum or maximum load configuration? The temperature set-point of _____ for the study _____ the production sterilization parameter of _____. Please provide the production and validation parameters, a description/diagram of the loading configurations used during production and validation data. **b(4)**
7. Information regarding the sterilization of product prior to performing the microbial ingress container-closure integrity test. It is not clear if the production cycle parameters were used or worst-case parameters.
8. The endotoxin specification _____ for the solvent is too high. Based on the specifications given for the lyophilized powder and the solvent, the total amount of endotoxin from the reconstituted product would far exceed the safety threshold of 350 EU per patient per hour. **b(4)**

Comments

1. The labels of the powder and solvent and the carton label do not state that the product is sterile.
2. In future studies, the current media fill acceptance criterion of ' _____' should be revised to be consistent with the Agency's current thinking. **b(4)**
Expression of acceptance criteria as a percentage of the number of units filled allows for an increasing number of contaminated test units as the size of the fill increases. However, the Agency feels the acceptable number of contaminated units should not increase in proportion to the number of vials in the media fill run. Therefore, the number of contaminated units in most media fills should be "0"; and although an occasional contamination should not be the basis of media fill failure, each contamination should be investigated and followed by appropriate action. A practical acceptance limit should be based upon the total number of contaminated units in a media fill run, irrespective of number of units filled in a media fill run.
3. It was observed that several documents and SOPs refer to previous editions of USP. All documents and acceptance criteria should be updated to conform to the most current USP.

Your response to the above requests should be submitted officially to your NDA 22-025. Please call at 301-796-1324 if further discussions are needed.

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/s/

Brenda Atkins
5/11/2006 08:07:50 AM
CSO

15/ 7-18-06

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)**

DATE RECEIVED: Apr. 11, 2006	DESIRED COMPLETION DATE:	OSE REVIEW #:
DATE OF DOCUMENT: Mar. 16, 2006	Jul. 18, 2006	06-0109
	PDUFA DATE: Aug. 1, 2006	

TO: Robert Justice, MD
Director, Division of Drug Oncology Products
HFD-150

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Totect™ (Dexrazoxane HCl for Injection) 500 mg/vial	SPONSOR: TopoTarget A/S
NDA #: 22-025	

RECOMMENDATIONS:

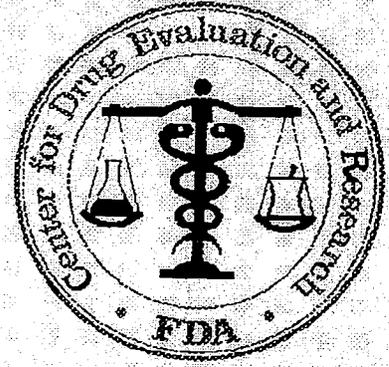
- DMETS has no objections to the use of the proprietary name, Totect. This is considered a final decision. However, if approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name Totect acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Pre-marketing Project Manager, at 301-796-0538.

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** April 28, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane) – Pharmacology/Toxicology Requests

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Please refer to your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006.

We have the following requests and would appreciate a rapid response:

1. Please submit tables of all the wound-area X day (AUC in $\text{mm}^2 \cdot \text{day}$) values calculated for individual animals for all non-clinical studies where that parameter was determined. We would prefer these tables in an easily readable electronic format such as SAS transfer files.
2. Please submit tables of all individual wound areas on given experimental days (mm^2 and day) for individual animals in all non-clinical studies where that parameter was measured in an easily readable electronic format such as SAS transfer files.

If these tables are also available in Microsoft Excel format, we would find them useful but not required.

Please call at 301-796-1324 if further discussions are needed.

esab@cder.fda.gov

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/s/

Brenda Atkins

4/28/2006 03:00:03 PM

CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-025

FILING COMMUNICATION

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

Dear Dr. McCulloch:

Please refer to your February 1, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Totect™ 500 mg Powder and Solvent for Injection (dexrazoxane as hydrochloride).

We also refer to your submissions dated January 31 and March 16, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 2, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Brenda Atkins

4/11/2006 08:01:37 AM

Signing for Acting Director, Robert L. Justice, M.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-025

NDA ACKNOWLEDGMENT

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

Dear Dr. McCulloch:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Totect™ 500 mg Powder and Solvent for Injection (dexrazoxane as hydrochloride).

Review Priority Classification: Priority (P)

Date of Application: January 31, 2006

Date of Receipt: February 1, 2006

Our Reference Number: NDA 22-025

Your application was filed on April 2, 2006, (60 days from the receipt date) in accordance with 21 CFR 314.101(a). The user fee goal date will be August 1, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-025

Page 2

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

If you have any questions, call Brenda Atkins, Consumer Safety Officer, at (301) 796-1324.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Brenda Atkins

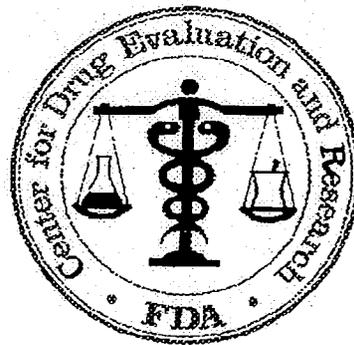
4/10/2006 12:58:24 PM

CORRECTION--DDR: This letter is a correction of the previous
acknowledgement letter entered in DFS Mon, 4-10-06 @12:29
pm 090014648062aaad8.pdf. Please MAIL THIS LETTER to the
sponsor. Signing for CPMS, Dotti Pease.

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** March 16, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane)

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Please refer to your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006.

Please submit a statement that all facilities (including contract analytical laboratories) are ready for inspection immediately. The statement should have been provided at the time of NDA submission. We wish to advise you that depending on the timeliness of getting your facilities ready and inspection scheduling, the facilities may or may not be inspected in time, although the Agency will make every effort not to impact the review clock.

Please call at 301-796-1324 if further discussions are needed.

rec'd response 3-22-06

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/s/

Brenda Atkins
3/16/2006 07:08:15 PM
CSO

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Dr. William McCulloch **From:** Brenda Atkins, Regulatory Project Manager

Fax: (919) 848-6495 **Fax:** (301) 796-9845

Phone: (919) 848-6495 **Phone:** (301) 796-1324

Pages, including cover sheet: 2 **Date:** March 1, 2006

Re: NDA 22-025 – Totect™ (dexrazoxane)

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Please refer to your New Drug Application (NDA) dated January 31, 2006, received February 1, 2006. Please provide a statement to the NDA indicating that all of the facilities (including contract facilities and test laboratories) are ready for GMP inspection.

Please call at 301-796-1324 if further discussions are needed.

*Need response
3-17-06 to COMIS*

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/s/

Brenda Atkins
3/1/2006 11:13:10 AM
CSO

Atkins, Brenda J

From: Hsieh, Yung Ao
Sent: Wednesday, March 01, 2006 9:45 AM
To: Atkins, Brenda J
Subject: Re: NDA 22-025

Brenda,

Please request the NDA applicant to provide a statement indicating that all of the facilities (including contract facilities and test laboratories) are ready for GMP inspection. Thanks.

Y. A. Hsieh

APPEARS THIS WAY ON ORIGINAL

TOPOTARGET

Robert Justice, MD, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

TopoTarget A/S
Symbion
Fruebjergvej 3
DK 2100 Copenhagen
Denmark
Tel: +45 39 17 83 92
Fax: +45 39 17 94 92
CVR-nr: 25695771

December 13, 2005

www.topotarget.com

**Subject: Original New Drug Application
Totect™ 500 mg Powder and Solvent for Injection**

Dear Dr. Justice:

Pursuant to 21 CFR 314.50(a)(5), TopoTarget A/S has transferred the responsibilities of US Agent for this application to Alba BioPharm Advisors, Inc. Alba BioPharm is responsible for all communication to and from the Agency. Please note the contact information provided below:

Dr. William McCulloch
US Agent/President
Alba BioPharm Advisors, Inc.
12109 Betts Lane
Raleigh, NC 27614
Phone/fax 919-848-6495
bmcculloch@albaadvice.com

Please contact Dr. McCulloch if you have any questions regarding this submission.

Sincerely,
TopoTarget A/S


Peter Buhl Jensen
Chief Executive Officer

TopoTarget UK Limited
87A Milton Park
Abingdon
Oxon, OX14 4RY
United Kingdom
Tel: +44 1235 443700
Fax: +44 1235 835557
Reg No. 2899713

TopoTarget Germany AG
Georg-Speyer-Haus
Paul-Ehrlich-Strasse 42-44
D-60596 Frankfurt am Main
Germany
Tel: +49 69 633 95 164
Fax: +49 69 633 95 352
HRB Frankfurt am Main 53432

Dexrazoxane

1.12.4 Request for Comments & Advice

Alyssa Carter

From: Bill McCulloch [bill.mcculloch@gloucesterpharma.com]
Sent: Monday, November 14, 2005 2:04 PM
To: Pease, Dorothy W
Subject: RE: IND #70,774 dexrazoxane (as "Totect") from TopoTarget A/S

Thanks very much, Dotti. That's very clear.

All the best,

Bill

>
> **From:** Pease, Dorothy W [mailto:PEASE@cder.fda.gov]
> **Sent:** Monday, November 14, 2005 1:46 PM
> **To:** Bill McCulloch
> **Subject:** RE: IND #70,774 dexrazoxane (as > "> Totect> ">) from TopoTarget A/S

> Here is the response from our chemistry staff.

>
> The expected amount of stability data for an NDA filing is 12 months of long term and 6 months of accelerated storage. However, we do file NDAs with limited stability data and accept timely stability updates during the course of the review. The sponsor may wish to provide stability updates for the drug and diluent during the course of the review. We will reference ICH Q1E for stability analysis and permissible extrapolations for the shelf life beyond the real time data. The expiration dating for the kit will be shorter of the expiration datings for the individual kit components (drug and diluent).

>
>
> Dotti

> -----Original Message-----

> **From:** Bill McCulloch [mailto:bill.mcculloch@gloucesterpharma.com]
> **Sent:** Monday, November 14, 2005 9:06 AM
> **To:** Pease, Dorothy W
> **Subject:** IND #70,774 dexrazoxane (as > "> Totect> ">) from TopoTarget A/S

> Dear Dotti:

> I know there has been a considerable amount of correspondence on the above between my colleagues at _____ and yourself. It might have been better to schedule a pre-NDA meeting (as I know you have advised us) but, for various practical reasons, TopoTarget would find this impossible. Therefore, as their agent in the US, they have asked me to ask you one technical, scientific question about the proposed NDA. b(4)

> They would like to present the active agent in kit form with a diluent as part of the package. While they have adequate stability etc. on the active agent, dexrazoxane (Totect), they may only be able to provide three months stability, including accelerated stability, on the diluent. The concern is that that might represent an issue which would be perceived as providing incomplete data and lead to a refusal to file the NDA. Could you advise us on this, please?

> As always, I appreciate your efforts very much.

> Best regards,

> Bill

> Dr. W. McCulloch
> President
> Alba BioPharm Advisors, Inc.,
> 12109 Betts Lane,

- > Raleigh NC 27614
- > (919) 848 6495 Phone and Fax
- > (919) 201 6699 Mobile
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Pease, Dorothy W

From: Pease, Dorothy W
Sent: Monday, September 26, 2005 8:27 AM
To: _____
Cc: bmcculloch@albaadvice.com
Subject: RE: TopoTarget NDA (pre-IND 70,774)

b(4)

I do have the attached results of your tradename consult which I tried faxing to Dr. McCulloch quite awhile ago, but didn't succeed.

If you let me know what your questions are, I can either answer them by e-mail, or at least line up the correct people for a telecon.

Thanks

Dotti

-----Original Message-----

From: _____
Sent: Friday, September 23, 2005 12:28 AM
To: dorothy.pease@fda.hhs.gov
Cc: bmcculloch@albaadvice.com
Subject: TopoTarget NDA (pre-IND 70,774)

b(4)

Dear Dotti,

I am contacting you on behalf of my client, TopoTarget A/S. TopoTarget has a product, _____ (dexrazoxane) targeted for the treatment of anthracycline extravasation during chemotherapy. The former proposed tradename was Topotect.

b(4)

A pre-NDA meeting was held with the Oncology Division on November 9, 2004. At that time a pre-IND number was assigned of 70,774. Subsequently, an IND was not filed because all of the clinical development has been conducted in Europe. In addition to the pre-NDA meeting, further advice was received from FDA on April 18, 2005 in response to a SPA request submitted March 3, 2005.

My company is helping TopoTarget with the writing of an NDA for . _____ The target submission date is the end of October 2005.

b(4)

I am emailing you to request a discussion regarding the NDA plans and also to resolve outstanding logistical issues regarding the submission. The US Agent for TopoTarget, Dr. William McCulloch of Alba BioPharm Advisors, will also be a part of these discussions.

Since you will be moving office in the first week of October, will you be available for a conference call prior to your move?

Best regards,

b(4)

b(4)

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FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Dr. W. McCulloch

Fax: 919 848-6495

FROM: Dotti Pease, Project Manager

Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 8-9-05

COMMENTS: Re: your pre-IND 70,774 for TopoTect, we have the attached comments from our consultative review re: the tradename _____

b(4)

Dotti

1. We have no objections to the use of the proprietary name, _____ However, we anticipate confusion between _____ and Zinecard because they share the same established name, Dexrazoxane Hydrochloride. This is considered a tentative decision and the you should be aware that this name with its associated labels and labeling must be reviewed upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

b(4)

2. We are concerned with potential confusion between _____ and Zinecard because they share the same established name, Dexrazoxane Injection, with different indications of use and different dosing regimens. Therefore, we recommend that an education campaign be developed and launched prior to the release of _____ in order to better inform the healthcare practitioners of the differences between these two products.

b(4)

3. We will recommend implementation of labeling revisions to minimize potential errors with the use of this product once the NDA is submitted. At that time we would expect you to submit the container labels and carton labeling for review and comment.

4. We find the proprietary name, _____, acceptable from a promotional perspective.

b(4)

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IND 70,774

TopoTarget A/S
c/o Aba BioPharm Advisors, Inc.
12109 Betts Lane
Raleigh, NC 27614

Attention: Dr. W. McCulloch

Dear Dr. McCulloch:

We refer to your pre-Investigational New Drug Application (pre-IND) for Topotect (dexrazoxane) i.v.

We also refer to your March 3, 2005, request for a special clinical protocol assessment, received March 4, 2005. The protocol is entitled "A Clinical Trial on Topotect (dexrazoxane) in the Treatment of Accidental Extravasation of Anthracycline Anti-cancer Agents."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. Does FDA have comments on the TT02 protocol, specifically focusing on endpoints and criteria for success?

FDA - Regarding the rationale and design of the study:

- a. We agree that there are wide differences in the role of early surgical intervention for this problem in different countries. Early surgical intervention is not standard in the U.S.
- b. We note that the dose recommended in the U.S. for dexrazoxane for cardioprotection uses a 10:1 ratio, thus a U.S. patient receiving 50 mg/m² of doxorubicin would receive 500 mg/m² dexrazoxane before the doxorubicin. This is one-half of the dose that you advise is recommended in the 1995 Chiron monograph and that you have chosen for your study.
- c. Dosing of 2500 mg/m² over 3 days is a cause for concern – it may be excessive.
- d. We note that dexrazoxane itself has toxicity including myelosuppression.
- e. In TT02, the primary endpoint is the proportion of "failures" observed, failure being a need for surgery or finding of necrosis ascertained by 2 independent observers. The decision to perform surgery may be influenced by each surgeon's prior experience. Evidence should be accessible to evaluate the surgeon's decision process.

- f. Color photography is planned at baseline, 4 weeks, and at 3 months and a ruler is to be included in the views along with coded patient ID. The photographs should allow an easy determination by an independent third party of the results. Please plan to submit these for our review. Lack of photo documentation may be considered by FDA as a treatment failure.
 - g. All patients should have a CBC weekly for four weeks following day 1 of the dexrazoxane infusions.
 - h. We also note that dexrazoxane IV injection is a generic product in the U.S.
 - i. We note that dexrazoxane is not FDA approved for use as a cardioprotectant with anthracyclines or anthracenediones except for doxorubicin.
 - j. How will you determine when to give the next dose of anthracycline?
2. We intend to proceed with the Statistical Analysis Plan as presented? Is this acceptable?

FDA - For the TT01 trial, no statistical inference can be made in a single arm study. Whether the endpoint (failure rate) and the size of the effect on this endpoint ($\leq 20\%$) are adequate is a clinical decision.

No statistical inference can also be made in the TT02 trial. Due to the difference between the current patient population and the historical patient population, any results from comparison between the failure rate observed from TT02 and the historical failure rate (35%) should be considered as supportive. Whether the endpoint (failure rate) and the size of the effect on this endpoint ($\leq 35\%$) are adequate is a clinical decision.

The upper limits of the two 95% confidence intervals can be compared with 20% and 35% respectively to determine if the two confidence intervals include 20% and 35% failure rates respectively.

3. Are the literature review as presented and the collected historical cases enough to allow the FDA to compare historical data with results of TT01 and TT02 and potentially to conclude that Topotec is efficacious for this indication?

FDA - We appreciate the effort you have made. This will be a review issue at the time you submit your results.

In addition, we have the following comments.

1. With your study mechanism in place, please consider subsequent study to explore lower doses and or fewer numbers of injections.
2. Because of the variability of historical controls and inability to conduct controlled trials in extravasation, the nonclinical studies are of particular importance. **Please submit the non-clinical study reports for review in support of the clinical results ASAP, i.e. in your initial IND.** A meeting re: the nonclinical studies will be needed once we have reviewed the nonclinical studies in the IND prior to NDA submission.
3. We strongly encourage you to submit the IND with these clinical and nonclinical studies ASAP.

4. Please note that the above comments do not constitute our acceptance of these protocols under our Special Protocol Assessment program, since the studies were already ongoing when we received the SPA. In addition, these are open label single arm studies where we believe bias would be difficult to control.
5. We recommend that the drug development program include pharmacokinetic sampling on Day 3 of the regimen. Such sampling could be incorporated in the current study, or in a different study, but pharmacokinetic data should be part of any NDA submission.
6. Please compile a contemporaneous listing of cases of extravasation in your hospital or similar ones in Denmark in which Dexrazoxane was not given, describing the circumstances of the extravasation and the management.
7. Please be sure to describe the details of the infusion procedure leading to the extravasation in each of your study patients.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Dotti Pease, Chief, Project Management Staff, at (301) 594-5742.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Richard Pazdur
4/18/05 11:39:08 AM

MEETING MINUTES

MEETING DATE: Nov. 9, 2004

TIME: 1:00

LOCATION: F

IND: pre-IND 70,774

Meeting Request Receipt Date: 8-20-04

FDA Response Date: 8-30-04

Briefing Document Receipt Date: 10-12-04

DRUG: Topotect (dexrazoxane) **INDICATION:** treatment of anthracycline extravasation during chemotherapy

SPONSOR: TopoTarget/Alba BioPharm Advisors **TYPE of MEETING:** pre-IND

FDA PARTICIPANTS: Richard Pazdur, M.D. Dir., DODP (pre-meeting)
Grant Williams, M.D., Dep. Dir., DODP
Ann Farrell, M.D., Medical Team Leader, DODP
Robert Kane, M.D., Medical Officer, DODP
Nallaperumal Chidambaram, Ph.D., Chem. Team Leader, DNDCI
Chengyi Liang, Ph.D., Chemistry Reviewer, DODP
David Morse, Ph.D., Pharm. Supervisor, DODP
Haleh Saber-Mahloogi, Ph.D., Pharmacologist, DODP
Gene Williams, Ph.D., Clin. Pharm. Reviewer, DODP
Raji Sridhara, Ph.D., Acting Stat. Team Leader, DODP (pre-mtg)
Shenghui Tang, Ph.D., Statistician, DODP
Dotti Pease, Project Manager, DODP

SPONSOR: Peter Buhl Jensen, M.D., CEO, TopoTarget
Maxwell Sehested, M.D., Chief Scientific Officer, TopoTarget
Annie Rasmussen, Dir. of Clinical Research, TopoTarget
Poul Knoblauch, Clinical Trial Manager, TopoTarget
Elisabeth Vang Carstensen, Ph.D., Head of Synthetic Chemistry, TopoTarget
Anne Vinding Sillemann, International Regulatory Affairs Man., TopoTarget
Ulla Hald Nuhl, Regulatory Manager, TopoTarget
Annemette Thougard, D.V.M., Ph.D., Head of *in vivo* studies, TopoTarget
Dr. William McCulloch, Pres., Alba BioPharm Advisors, Inc.

MEETING OBJECTIVES: Discuss proposed IND and sponsor's questions

BACKGROUND: Dexrazoxane, marketed as Zinecard by Pfizer, is commercially available in the U.S. for the reduction of cardiotoxicity from doxorubicin only. It is marketed as Cardioxane by Chiron outside of US for the same indication. The 2 marketed formulations are manufactured

via different processes but have similar specifications. Both formulations are a sterile, lyophilized hydrochloride acid salt. Dexrazoxane is a chelating agent and catalytic inhibitor of Topo II.

TopoTarget received Orphan Drug designation for dexrazoxane for the treatment of anthracycline extravasation during chemotherapy on March 25, 2004. Their proposal is to use two open-label randomized European trials (TT01 with Chiron product completed and TT02 with Pfizer product ongoing) with a total of 53 patients and submit the results (probably with less than 53 patients) in an NDA.

After the internal pre-meeting on Nov. 2, the FDA draft responses were faxed to the sponsor, who chose to proceed with the face-to-face meeting for clarification of the responses. Discussion at the meeting is indicated below in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. TT01 and TT02 have been conducted with dexrazoxane-containing products from two different companies. A comparison of Cardioxane and Zinecard's identity and purity has been performed. The conclusion of the study was that for clinical purposes Cardioxane and Zinecard are pharmaceutical equivalents. The studies demonstrating pharmaceutical equivalence of the two formulations of dexrazoxane, Cardioxane and Zinecard, are summarized in section 5.1 and 5.2.1.2.

Does the FDA agree that the two formulations of Topotect, namely Cardioxane and Zinecard, used in the clinical trial programs TT01 and TT02, for the purpose of treatment of anthracycline extravasation during chemotherapy, can be considered identical?

FDA - Even though you claim that Zinecard and Cardioxane are pharmaceutically equivalent, we cannot explain the observed difference in pH values (0.5) when they are reconstituted in water. You should explain and justify the observed difference in pH.

DISCUSSION: Yes, as long as the products are therapeutically equivalent, studies with both products would be usable for the NDA. The NDA would be submitted with one product from one supplier.

2. Dexrazoxane has been in clinical use since the early 1970's and there is extensive literature describing its non-clinical and clinical aspects (see sections 5.2 and 5.3). TopoTarget believes that in view of these data already available for the active moiety, dexrazoxane, no further non-clinical studies are necessary for the indication under consideration. Does the FDA agree?

FDA – We are assuming you are planning on submitting a 505(b)(2) NDA. You

should be aware that FDA's implementation of 505(b)(2) is currently being challenged in the courts.

Your NDA will need to contain sufficient information to address labeling for overdose, genetic and/or carcinogenic potential, and reproductive toxicities (fertility, embryofetal development, post-natal development) of dexrazoxane. Information to address these issues may be obtained from published literature, toxicology studies or prior human use experience.

DISCUSSION: Sponsor will provide available information in the NDA. No carcinogenicity studies are available or planned. The division does not anticipate that carcinogenicity studies would be required for this indication.

- 3 Would the two studies – TT01 and TT02, both European studies with a combined total of a minimum of 53 evaluable patients – be a satisfactory efficacy database for NDA approval?

FDA - Possibly. Unless the results are striking, a comparative control would be required. We will need clear definition of your prospectively planned historical control group, cohort control, or other control group in your protocol analysis plan – i.e., information on the number of extravasations and results of management at the institutions before your study started.

We would have to be able to review the cases in detail to understand approximately how much anthracycline was given, whether the anthracycline was being infused in a dilute form or pushed, the infusion technique, type of venous access, how large the induration area was in each case, and the time from infiltration to administration of dexrazoxane.

In addition, please provide results of blood counts during that cycle of treatment as well as the one before and after the cycle with the extravasation. The dose of dexrazoxane may be excessive and toxicity assessments are important as well as efficacy.

In addition, we will want to review detailed study reports of your nonclinical findings.

We strongly recommend that you submit a Special Protocol assessment for your proposed registration trial(s). See Guidance for Industry – Special Protocol Assessments at www.fda.gov/cder/guidance/index.htm

DISCUSSION: Sponsor will address above issues in NDA. If submitted, the SPA or follow-up meeting request should include the proposed analytical methods and clear description of the control(s). We would like some lead-in time before this request so we have the opportunity to get feedback from consultant(s) re: the protocols, SAP, and

control(s) to be used to demonstrate the clinical benefit of the dexrazoxane treatment.

4. TT01 and TT02 are European studies and TopoTarget does not intend to conduct any US studies before approval. Is this acceptable to the FDA?

FDA - Studies do not have to be performed in the U.S.

5. In view of the rarity of the condition being addressed, there are no randomized studies available and the Sponsor does not intend to conduct any such studies. Is this acceptable to the FDA?

FDA - Possibly. See above.

6. Since the success rate in the TT02 study has been very promising so far - only 1 failure out of 18 evaluable patients – and due to the fact that the accrual to TT02 is slow, the Sponsor might want to submit the NDA before all patients have been included in the TT02 trial, meaning that there would be less than 53 evaluable patients at the time of submission. Would such an approach be acceptable to the FDA if the full database were to be submitted upon completion of TT02?

FDA - See reply to question 3. Careful photographic documentation may also be helpful to support your results.

DISCUSSION: Sample photos provided.

7. Does the FDA accept the proposed indication as expressed in the Orphan Drug Designation: “Treatment of anthracycline extravasation during chemotherapy”?

FDA – You will need to provide data or other information on whether your drug protects against all anthracyclines rather than just doxorubicin.

DISCUSSION: Sponsor will have clinical information on epirubicin and doxorubicin and nonclinical data on other anthracyclines. FDA – this will be a review issue in the NDA.

8. Since Topotect is intended for treatment of anthracycline extravasation during chemotherapy, a serious condition, and Topotect has demonstrated the potential to address this unmet medical need, the Sponsor believes that Topotect qualifies for consideration of fast track approval. Does the FDA agree?

FDA - This request should be submitted to the IND, if and when it is submitted. We would evaluate your support for this at the time of IND submission. If you are referring to priority review, this will be determined at the time the NDA is submitted.

We strongly recommend you request a pre-NDA meeting prior to submission of an NDA.

DISCUSSION: Sponsor is considering submitting a rolling review NDA, which requires Fast Track Designation. FDA – we can talk about this more later, but we don't see any clear benefit at this time.

ADDITIONAL FDA COMMENTS:

No statistical inferences can be made in a single arm study unless a null hypothesis is pre-specified stating the minimum effect that is clinically meaningful.

ACTION ITEMS:

1. Sponsor will consider our recommendations and possibly submit another meeting request or SPA for review of the proposed statistical analysis plan, especially the proposal for defining the controls.
2. Sponsor will submit a request for a pre-NDA meeting once studies are completed to discuss formatting and other issues re: the NDA.

Concurrence Chair:

Dotti Pease
Chief, Project Management Staff

Ann Farrell, M.D.
Medical Team Leader

ATTACHMENTS: FDA Standard EOP2 Bullets (not discussed)

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FINAL PROTOCOLS

Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)** in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF) should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs till 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering

your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2 Year	>2-#12
	12-16	17-64	≥65
Race:	White	Black	Asian
	Other		

CHEMISTRY

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

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/s/

Ann Farrell

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