

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-025**

**CHEMISTRY REVIEW(S)**

# Official Memorandum

**To:** NDA 22-025  
**Through:** Ravi Harapanhalli, Ph.D.  
**From:** Sarah C. Pope, Ph.D.  
**Date:** 8/30/2007  
**Re:** CMC Review of Complete Response dated 18-JUN-2007

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Reference is made to the Agency's Approvable letter dated 01-JUN-2007, which specified two outstanding CMC deficiencies for NDA 22-025. Reference is also made to the Applicant's response to the Approvable letter, dated 19-JUN-2007, and the Applicant's amendment dated 06-JUL-2007. The two outstanding CMC deficiencies are listed below, followed by the respective resolutions:

**Deficiency #1:** During a recent inspection of the Pharma 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.

**Resolution for Deficiency #1:** As part of the CMC review of this complete response, all proposed manufacturing, testing, packaging, and labeling sites were re-entered into the Establishment Evaluation System for confirmation of cGMP compliance status. Initially, one of the proposed manufacturing sites, Ben Venue Laboratories, received a withhold recommendation (13-AUG-2007) from the Cincinnati field office and the Office of Compliance. However, based on subsequent extensive discussions between the ONDQA review division (Ravi Harapanhalli and Sarah Pope) and the Office of Compliance, the previous withhold recommendation was amended to an acceptable recommendation on 29-AUG-2007 due to the case-specific nature of this drug. As a result, the Office of Compliance issued an overall acceptable recommendation for the application on 29-AUG-2007.

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

- a) The established name of the drug has been revised to "dexrazoxane" but the recommended statement "Each vial of dexrazoxane for injection contains 589 mg of dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane" is not captured on the side panels.
- b) The storage statement does not include the temperature range allowed for excursions, i.e., 15-30°C. Therefore, the following statement should be included: "Excursions permitted between 15-30°C."

**Resolution for Deficiency #2:** The Applicant has complied with the two recommendations and has provided acceptable revised container/carton labeling as part of the 18-JUN-2007 complete response. The final container/carton labeling is attached.

APPEARS THIS WAY ON ORIGINAL

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

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Sarah Pope  
8/30/2007 03:34:14 PM  
CHEMIST

Ravi Harapanhalli  
8/30/2007 03:38:27 PM  
CHEMIST

NDA 22-025 Totect (Dexrazoxane\*) For Injection

\*Contains 589 mg dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane

Branch Chief Memo

Ravi S. Harapanhalli, Ph.D.

May 24, 2007-05-24

CMC Review:

Leon Epps Ph.D. reviewed the CMC portion of the NDA and his review was signed off into the DFS on May 22, 2007. Although all CMC deficiencies were adequately addressed, his review made note of pending compliance recommendation and pending revisions to the container and cartons.

Overall recommendation:

The Office of Compliance recommended "withhold" for this NDA on May 23, 2007. Pharma Hameln site was deemed out of compliance during a recent inspection. Pharma Hameln was listed as the primary manufacturing site for the \_\_\_\_\_ Ben Venue Laboratory was also listed as an alternative manufacturing site and was deemed acceptable for GMP compliance. The withhold recommendation for the primary manufacturing site is a serious concern and hence from CMC perspective, we will recommend "approvable" for this NDA. The following deficiency needs to be included in the action letter:

b(4)

*'You have failed to demonstrate satisfactory cGMP compliance for the Pharma Hameln GMBH manufacturing facility. Several deficiencies noted during a recent inspection led to a withhold recommendation from the Office of Compliance. Demonstration of adequate cGMP compliance is required before the approval of the NDA.'*

Carton and Container labels:

The revised container and carton labels submitted to the Agency on May 23, 2007 did not incorporate all the recommendations. Specifically, the following recommendations have not been incorporated in the updated container and carton labels.

1. The established name of the drug has been revised to "dexrazoxane" but the recommended statement "Each vial of dexrazoxane for injection contains 589 mg of dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane" is not captured on the side panels.
2. The storage statement does not include the temperature range allowed for excursion, i.e. 15-30°C. Therefore, the following statement should be included: "Excursions permitted between 15-30°C."

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/s/

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Ravi Harapanhalli  
5/24/2007 03:28:26 PM  
CHEMIST



**NDA 22-025**

**Totect™ (dexrazoxane for injection)**

**Topo Target A/S**

**Leon A. Epps, Ph.D.**

**Office of New Drug Quality Assessment (DPAMS/Branch V)**

**CMC Review of NDA (505b2)**

**For OND Division of Drug Oncology Products (HFD-150)**



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# CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-025
2. REVIEW 02
3. REVIEW DATE: May 22, 2007
4. REVIEWER: Leon A. Epps, Ph.D.
5. PREVIOUS DOCUMENTS:
  - a) Initial Quality Assessment dated February 1, 2006
  - b) Complete CMC Review Number #1 dated July 25, 2007

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	January 31, 2006
Amendment-BC FDA Inspection readiness claimed for all manufacturers but _____	March 17, 2006
Amendment-BC _____ ready for FDA inspection in January 2007.	March 31, 2006
Amendment-BC Request adding _____ as alternate supplier for _____	June 5, 2006
Amendment-BC Stability Update.	June 9, 2006
Amendment-BC revised readiness status for FDA inspection of Integrated Commercialization Solutions (Brooks, Kentucky) to August 1, 2006.	June 14, 2006
Amendment-BC _____	July 5, 2006
Amendment-BZ PDF Labeling Files.	July 6, 2006
Amendment-BC revised readiness status for FDA inspection of Integrated Commercialization Solutions (Brooks, Kentucky) to July 19, 2006 and modified validations methods to meet USP.	July 19, 2006

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b(4)

b(4)

6. SUBMISSION(S) BEING REVIEWED:

Amendment-BZ Complete Response	November 22, 2006
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7. NAME & ADDRESS OF APPLICANT:

Name: Topo Target A/S

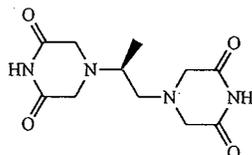


# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



The molecular formula is  $C_{11}H_{16}N_4O_4$ ; the molecular weight is 268.3.

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED			DATE REVIEW COMPLETED	COMMENTS
	II	/		1	Adequate	April 10, 2007	L. Epps
	II			3	Adequate	January 31, 2006	M. Shaikh, HFD-630
	III			3	Adequate	October 13, 2006	L. Epps
	III			3	Adequate	July 7, 2006	L. Epps
	III			4	Adequate	April 10, 2007	L. Epps

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	070774	Original IND dated January 31, 2006
ANDA	076068	Dexrazoxane for Injection 250 mg and 500 mg, micro reviews dated December 17, 2003 and March 12, 2004

### 18. STATUS

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	pending	May 23, 2007	R. Harapanhalli
Pharm/Tox	Not consulted		
Biopharm	Not consulted		
LNC	N/A Conventional dosage form	N/A	N/A
Methods Validation	Methods do not require FDA lab validation	July 14, 2006	L. Epps
ODS/DMETs	DMETs review in DFS	May 16, 2007	Judy Park
EA	Categorical exclusion justified	July 14, 2006	L. Epps
Microbiology	Recommend approval	April 5, 2007	Anastasia Lolas (Review in DFS)

APPEARS THIS WAY ON ORIGINAL



Chemistry Assessment Section

The Chemistry Review for NDA 22-025

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert, and upon an acceptable recommendation from the Office of Compliance regarding cGMP compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s):

Dexrazoxane has been in clinical use since the early 1970's and has been marketed in the USA as the product Zinecard, by Pfizer (formerly Pharmacia) for the prevention of cardiomyopathy associated with doxorubicin administration since 1995. Bedford supplies a generic version of the drug and Chiron supplies the drug outside of the USA as Cardioxane.

Dexrazoxane is synthesized from the commercially available (S)-1, 2 diaminopropane-N,N,N',N'-tetraacetic acid which provides the backbone of the drug substance molecule.

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The molecular formula is  $C_{11}H_{16}N_4O_4$  corresponds to a molecular weight of 268.3. Dexrazoxane is a white to off-white powder which melts at  $194 \pm 3$  °C. It is soluble in dioxane and 0.1N HCl, sparingly soluble in water, tetrahydrofuran, citrate buffer at pH 4.0, phosphate buffer at pH 7.0, and borate-potassium chloride sodium hydroxide buffer at pH 9.0. The acid dissociation constants, pKa, are 2.5 (for the tertiary piperazine nitrogen) and 9.7 (for the nitrogen imide). The log P is -2.135.

The finished product is supplied in a sterile form for intravenous infusion only following mixing and diluting. Each carton contains twenty 50 mL glass vials. Ten vials contain 589 mg dexrazoxane hydrochloride lyophilized powder equivalent to

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b(4)

## Chemistry Assessment Section

500 mg dexrazoxane. The other 10 vials contain diluent (0.0167M Sodium Lactate Injection, USP). Each vial of dexrazoxane for injection is closed with an aluminum flip-off cap covered with a dark red overcap. Each vial of diluent is closed with an aluminum flip-off cap covered with a white overcap.

When reconstituted as directed, the admixture contains dexrazoxane and the following excipients: hydrochloric acid, sodium lactate, water for injection, sodium hydroxide and lactic acid. The admixture should be further diluted in 0.9% NaCl prior to administration to patients.

This review is on the response to an approvable action dated August 1, 2006 and includes a resubmission of Chemistry, Manufacturing and Controls information from a new drug product manufacturer. The resubmission was filed on December 13, 2006.

**B. Description of How the Drug Product is Intended to be Used:**

The drug product (Totect™) is indicated for the treatment of extravasation that occurs during anthracycline chemotherapy and is available in cartons containing 10 vials of 500 mg dexrazoxane and 10 vials of 50 mL solvent for injection to provide 3 days of treatment for one patient. The product consists of a glass vial with a lyophilized powder and a glass vial that contains the sodium lactate for injection (USP) solvent for reconstitution. The lyophilized product is \_\_\_\_\_ filled while the solvent is \_\_\_\_\_ filled. Before infusion, each vial of Totect™ 500 mg powder must be mixed with the specified diluent, a.k.a., 50 mL Totect™ solvent for injection. The mixed solution should be further diluted in 1000 mL 0.9% NaCl. Totect™ should be given once daily for 3 consecutive days. The first infusion should be initiated as soon as possible and within the first six hours after extravasation. The recommended dose is 1000 mg/m<sup>2</sup> on Days One and Two (maximum recommended dose of 2000 mg on each of the first two days) and is 500 mg/m<sup>2</sup> on Day Three (maximum recommended dose of 1000 mg on the third day).

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Dexrazoxane has been in clinical use since the early 1970's and has been marketed as the product Zinecard, by Pfizer (formerly Pharmacia) for the indication of Prevention of cardiomyopathy associated with doxorubicin administration in the USA since 1995. Bedford supplies a generic version of the drug and Chiron supplies the drug outside of the USA as Cardioxane.

**C. Basis for Approvability or Not-Approval Recommendation:**

In order for this NDA to be recommended for Approval from Chemistry, Manufacturing, Controls standpoints, the following three items needs to be satisfactorily resolved:

- 1) Acceptable container/carton labeling should be submitted. Container/carton comments were sent to the applicant on May 21, 2007. Response is pending see page 75 of this review.
- 2) Acceptable final labeling, including the Patient Information and Physician's Package Insert, should be submitted.



Chemistry Assessment Section

- 3) An acceptable recommendation from Compliance. Pending. See page 4 of this review.

III. Administrative

A. Reviewer's Signature

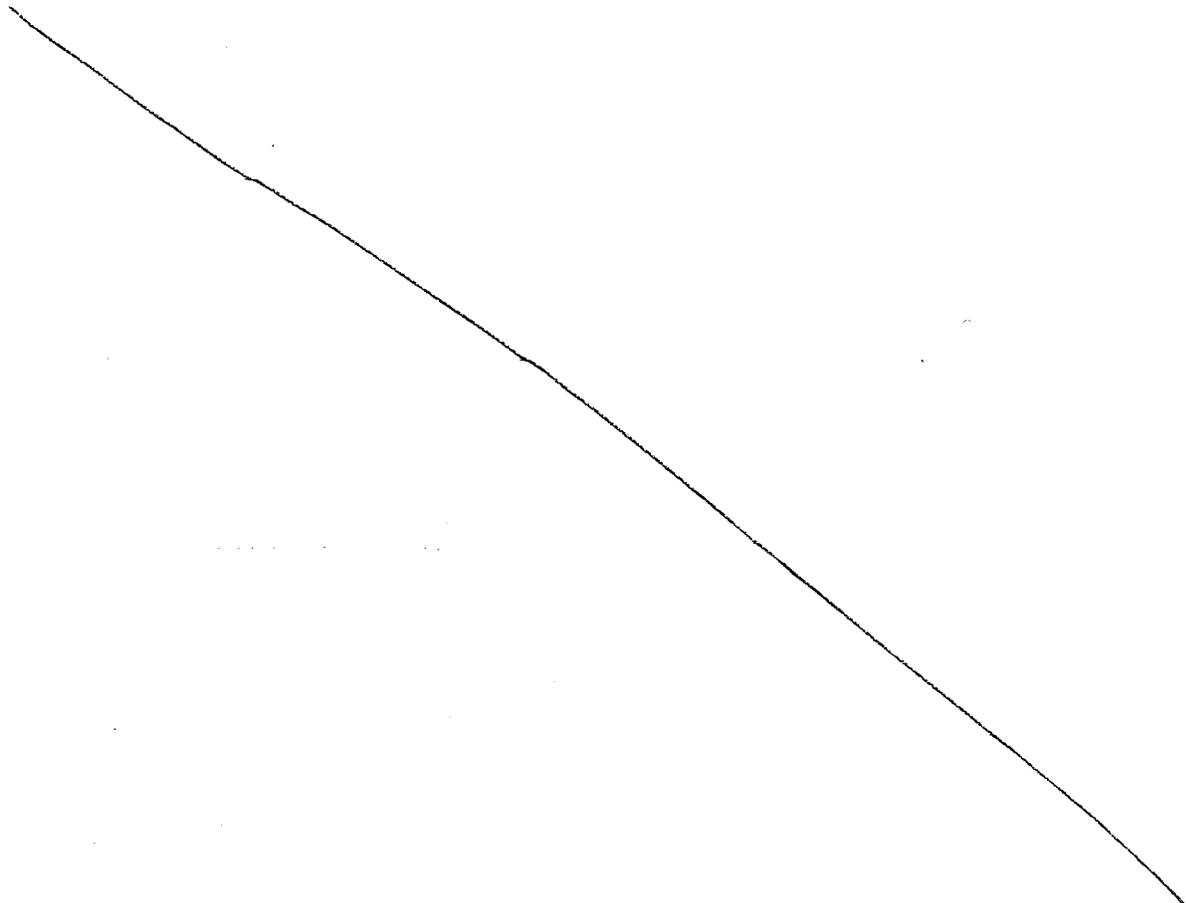
Leon A. Epps, Ph.D., Reviewer ONDQA

B. Endorsement Block

Chemist Name/Date: Leon A. Epps, Ph.D. Same date as draft review  
Chemistry Division Director Name/Date: Richard T. Lostritto, Ph.D.  
Project Manager Name/Date: Karl Stiller

C. CC Block

Brenda Atkins, PM, HFD-150



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**  
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/s/  
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Leon Epps  
5/22/2007 05:26:30 PM  
CHEMIST

Richard Lostritto  
5/22/2007 05:38:20 PM  
CHEMIST



**NDA 22-025**

**Totect™ (Dexrazoxane for Injection)**

**Topo Target A/S**

**Leon A. Epps, Ph.D.**

**Office of New Drug Quality Assessment (DPAMS/Branch V)**

**CMC Review of NDA (505b2)**

**For OND Division of New Drug Oncology Products**



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    C. CC Block ..... 11

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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..... 11

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    P DRUG PRODUCT [Name, Dosage form] ..... 18

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    R REGIONAL INFORMATION ..... 54

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    B. Environmental Assessment Or Claim Of Categorical Exclusion ..... 57

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# CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-025
2. REVIEW 01
3. REVIEW DATE: July 14, 2006
4. REVIEWER: Leon A. Epps, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA

January 31, 2006

Amendment-BC FDA Inspection readiness claimed for all manufacturers but \_\_\_\_\_

March 17, 2006

b(4)

Amendment-BC \_\_\_\_\_ ready for FDA inspection in January 2007.

March 31, 2006

Amendment-BC Request adding \_\_\_\_\_ as alternate supplier for \_\_\_\_\_

June 5, 2006

b(4)

Amendment-BC Stability Update.

June 9, 2006

Amendment-BC revised readiness status for FDA inspection of Integrated Commercialization Solutions (Brooks, Kentucky) to August 1, 2006.

June 14, 2006

Amendment-BC \_\_\_\_\_

July 5, 2006

b(4)

Amendment-BZ PDF Labeling Files.

July 6, 2006

Amendment-BC revised readiness status for FDA inspection of Integrated Commercialization Solutions (Brooks, Kentucky) to July 19, 2006 and modified validations methods to meet USP.

July 19, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Topo Target A/S



## Chemistry Review Data Sheet

Address: Symbion Science Park  
Fruebjergvej 3  
DK-2100 Copenhagen  
Denmark

Representative: Dr. William McCulloch  
Alba BioPharm Advisors, Inc.  
12109 Betts Lane, Raleigh, NC 27614

Telephone: 919-848-6495

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Totect™  
b) Non-Proprietary Name: Dexrazoxane for Injection  
c) Code Name/#: N/A  
d) Chem. Type/Submission Priority (ONDQA only):  
(i) Priority

9. LEGAL BASIS FOR SUBMISSION: 505b2

10. PHARMACOL. CATEGORY: Treatment of anthracycline extravasation during chemotherapy

11. DOSAGE FORM: Powder for Injection

12. STRENGTHS/POTENCIES: 500 mg

13. ROUTE OF ADMINISTRATION: Intravenous Administration

14. Rx/OTC DISPENSED: X Rx \_\_\_ OTC

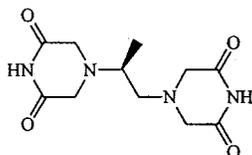
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_ SPOTS product – Form Completed

x Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



The molecular formula is C<sub>11</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>; the molecular weight is 268.3.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCE D			DATE REVIEW COMPLE TED	COMMEN TS
	II	/	/	1	Adequate	June 21, 2006	L. Epps
	III			4	Adequate	July 14, 2006	L. Epps
	III			1	Inadequate	July 12, 2006	A. Lolas
	III			3	Adequate	July 7, 2006	L. Epps

b(4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

IND	70774	Original IND dated January 31, 2006

### 18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	pending		
Pharm/Tox	Not consulted		
Biopharm	Not consulted		
LNC	N/A	N/A	N/A
Methods Validation	Methods will be submitted post-approval	July 14, 2006	L. Epps
OPDRA	DMETS comments pending	July 14, 2006	L. Epps
EA	Categorical exclusion justified	July 14, 2006	L. Epps
Microbiology	Approvable	July 12, 2006	Anasthasia Lolas (Review in DFS)

APPEARS THIS WAY ON ORIGINAL



Chemistry Assessment Section

The Chemistry Review for NDA 22-025

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is approvable from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. . None

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s):

Dexrazoxane has been in clinical use since the early 1970's and has been marketed as the product Zinecard, by Pfizer (formerly Pharmacia) for the indication of Prevention of cardiomyopathy associated with doxorubicin administration in the USA since 1995. Bedford supplies a Generic version of the drug and Chiron supplies the drug outside of the USA as Cardioxane.

Dexrazoxane is synthesized from the commercially available (S)-1, 2 diaminopropane-N,N,N',N'-tetraacetic acid which provides the backbone of the drug substance molecule.

\_\_\_\_\_

b(4)

Dexrazoxane is isolated as a white to off-white powder, with a melting point of  $194 \pm 3$  °C. It is soluble in dioxane and 0.1 N HCl, sparingly soluble in water, tetrahydrofuran, citrate buffer at pH 4.0, phosphate buffer at pH 7.0, and borate-potassium chloride sodium hydroxide buffer at pH 9.0.

\_\_\_\_\_

b(4)

The reconstituted solution should be diluted with 0.9% NaCl solution prior to administration. Each vial of dexrazoxane is

## Chemistry Assessment Section

closed with \_\_\_\_\_ an aluminum flip-off cap and should be stored below 25°C (77°F).

b(4)

Excipients for the dexrazoxane drug product (Totect™) \_\_\_\_\_ hydrochloric acid \_\_\_\_\_  
 \_\_\_\_\_ Sodium lactate \_\_\_\_\_ lactic acid \_\_\_\_\_  
 \_\_\_\_\_ sodium hydroxide \_\_\_\_\_ and water for injection \_\_\_\_\_

b(4)

## B. Description of How the Drug Product is Intended to be Used:

The drug product (Totect™) is indicated for the treatment of extravasation that occurs during anthracycline chemotherapy and is available in cartons containing 10 vials of 500 mg dexrazoxane and 10 vials of 50 mL solvent for injection to provide 3 days of treatment for one patient. The product consists of a glass vial with a lyophilized powder and a glass vial that contains the sodium lactate for injection (USP) solvent for reconstitution. The lyophilized product is \_\_\_\_\_ filled while the solvent is \_\_\_\_\_ filled \_\_\_\_\_ Before infusion, each vial of Totect™ 500 mg powder must be mixed with 50 mL Totect™ solvent for injection. The mixed solution should be further diluted in 1000 mL 0.9% NaCl. Totect™ should be given once daily for 3 consecutive days. The first infusion should be initiated as soon as possible and within the first six hours after extravasation. The recommended dose is 1000 mg/m<sup>2</sup> on Days One and Two (maximum recommended dose of 2000 mg on each of the first two days) and is 500 mg/m<sup>2</sup> on Day Three (maximum recommended dose of 1000 mg on the third day).

b(4)

Dexrazoxane has been in clinical use since the early 1970's and has been marketed as the product Zinecard, by Pfizer (formerly Pharmacia) for the indication of Prevention of cardiomyopathy associated with doxorubicin administration in the USA since 1995. Bedford supplies a Generic version of the drug and Chiron supplies the drug outside of the USA as Cardioxane.

## C. Basis for Approvability or Not-Approval Recommendation:

Unresolved inspectional issues:

NDA was beset with several discrepancies and issues with the listing of manufacturing and testing sites and statements on their readiness for inspection. Two separate reminders were sent to the firm on March 1, 2006, and March 16, 2006 asking the firm to provide a statement regarding readiness for inspection of the listed sites. In an amendment dated March 17, 2006, the firm provided the following responses.

- The \_\_\_\_\_ manufacturer \_\_\_\_\_ would be ready for inspection in 3 months. (Subsequently this site was inspected and deemed acceptable for cGMP compliance.)

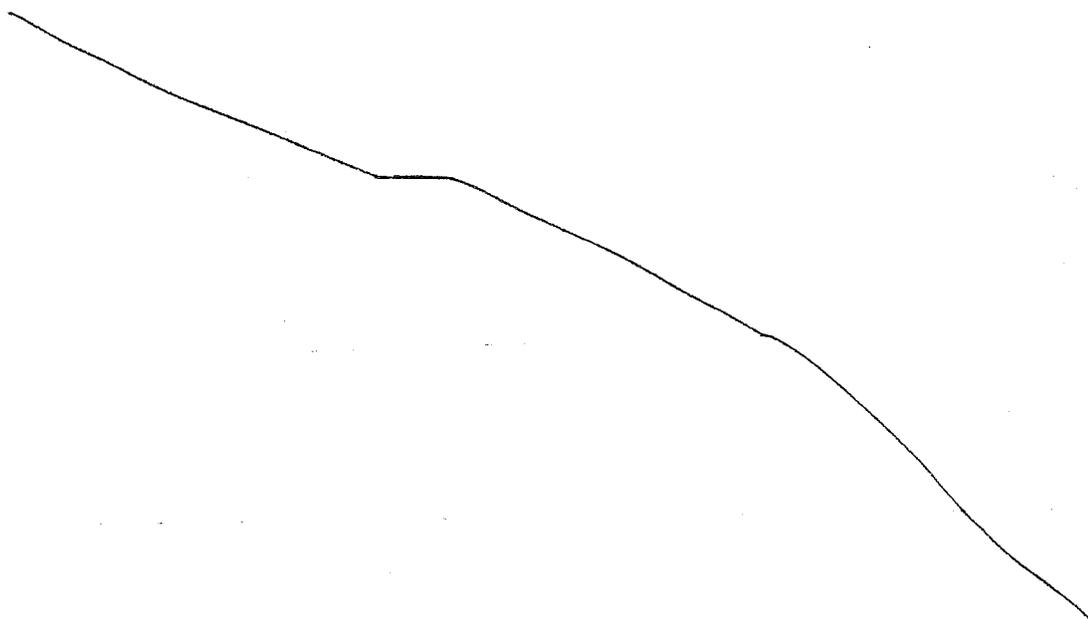
b(4)

## Chemistry Assessment Section

- The \_\_\_\_\_ manufacturer \_\_\_\_\_ and the testing sites \_\_\_\_\_ Integrated Commercialization Solutions, USA were all listed as being ready for inspection. **b(4)**
- The \_\_\_\_\_ manufacturer Hameln, Pharma., GmbH, Germany and the \_\_\_\_\_ Integrated Commercialization Solutions (ICS), USA were also listed as being ready for inspections. **b(4)**
- The inspection readiness statement on the subcontractor to \_\_\_\_\_ that carries out \_\_\_\_\_ was pending. However, an amendment dated March 31, 2006 clarified that this facility would not be ready for inspections until January, 2007. **b(4)**

The District Office recommended "withhold" for Integrated Commercialization Solutions, USA on May 4, 2006 since the firm was not ready for inspections despite a statement of readiness dated March 17, 2006. Subsequently, in an e-mail dated July 19, 2006, the firm indicated that the ICS facility was now ready for inspections, however, the firm was asked to submit a formal amendment to this effect. Meanwhile, the EES recommendation was changed from "WH" to "PN" for this facility.

To date, \_\_\_\_\_ ICS are listed with "PN" status in the EES. The inspections of the first three sites, which are foreign sites, have been scheduled since April 3, 2006 and that for the ICS has been assigned on July 20, 2006. Also, as indicated above, \_\_\_\_\_ that carries out \_\_\_\_\_ will not be ready until January, 2007. Therefore, it is unlikely that complete compliance action could be taken within the PDUFA date of August 1, 2006. Hence, overall compliance recommendation in this review cycle will not impact our "AE" recommendation for this NDA. **b(4)**





Chemistry Assessment Section

Unresolved issues in applicant's e-mail dated July 19, 2006:

As indicated above, the firm has not submitted an official amendment indicating that ICS facility is ready for inspections. Additionally, issues on chemistry documents of validation methods not using USP methods have not been resolved. The e-mail response indicates that all methods have been changed to refer to current USP. The firm stated that since the changes were merely in validation methods and were not substantive, it would be cumbersome to re-submit all the documents at this late stage in the review cycle. Therefore, the firm proposed that the Agency accept some kind of blanket assurance that all methods are now USP and that the corrected documents would then be re-submitted after the action date of August 1, 2006.

This approach is unacceptable. It is expected that all revised CMC documents of validation methods be submitted and be reviewed and accepted before an NDA can be approved.

Unresolved issues with microbial product quality:

The microbiology reviewer, Anssthasia Lolos in her review dated July 12, 2006 recommended "AE" action pending resolution of microbiology deficiencies, namely incomplete studies on product-specific filter bacterial retention for the lyophilized product and inconsistencies and inadequate data submitted in support of the sterilization of the solvent. The reviewer opined that the risk to the patient is high because without adequate sterilization validation data, the sterility of the product is not assured.

b(4)

Overall recommendation:

In view of the above discussion, the NDA is approvable from CMC perspective. The applicant should fully resolve and address the above deficiencies before the NDA can be approved.

III. Administrative

A. Reviewer's Signature

Leon A. Epps, Ph.D., Reviewer ONDQA

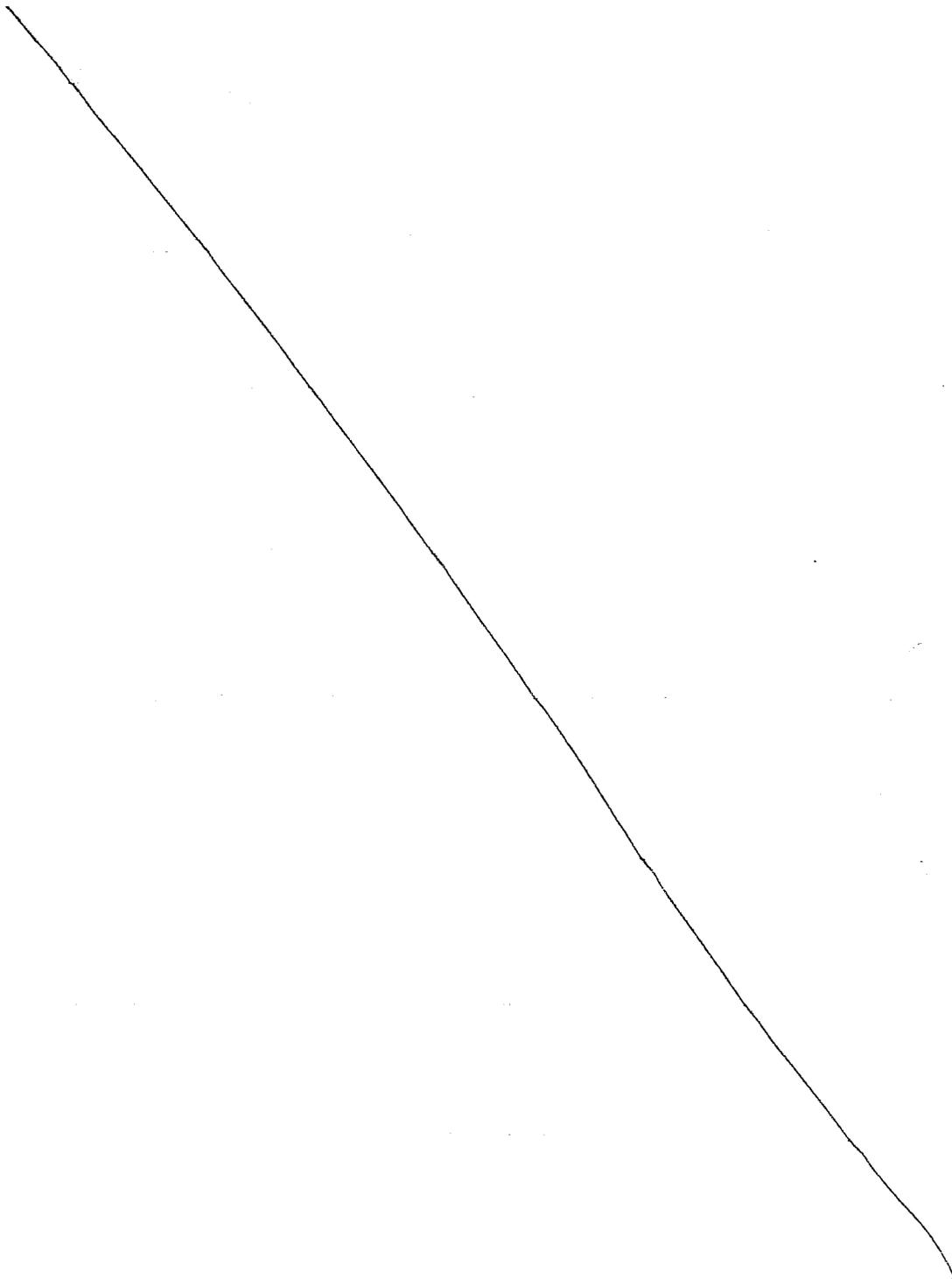
B. Endorsement Block

Chemist Name/Date: Leon A. Epps, Ph.D. Same date as draft review  
Chemistry Branch Chief Name/Date: Ravi S. Harapanhalli, Ph.D.  
Project Manager Name/Date: Karl Stiller



Chemistry Assessment Section

C. CC Block



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Leon Epps  
7/25/2006 03:14:05 PM  
CHEMIST

Ravi Harapanhalli  
7/25/2006 03:33:51 PM  
CHEMIST

CMC Branch Chief Memo: NDA 22-025

July 24, 2006

Ravi S. Harapanhalli, Ph.D.  
Chief, Branch V, DPAMS, ONDQA

Overall recommendation:

The NDA is approvable from CMC perspective. Please refer to the CMC review by Leon Epps, Ph.D. in the DFS.

Introduction and background:

The drug product (Totect™) is indicated for the treatment of extravasation that occurs during anthracycline chemotherapy and is available in cartons containing 10 vials of 500 mg dexrazoxane and 10 vials of 50 mL solvent for injection to provide 3 days of treatment for one patient. The product consists of a glass vial with a lyophilized powder and a glass vial that contains the sodium lactate for injection (USP) solvent for reconstitution. The lyophilized product is \_\_\_\_\_ filled while the solvent is \_\_\_\_\_ filled. Before infusion, each vial of Totect™ 500 mg powder must be mixed with 50 mL Totect™ solvent for injection. The mixed solution should be further diluted in 1000 mL 0.9% NaCl. Totect™ should be given once daily for 3 consecutive days. The first infusion should be initiated as soon as possible and within the first six hours after extravasation. The recommended dose is 1000 mg/m<sup>2</sup> on Days One and Two (maximum recommended dose of 2000 mg on each of the first two days) and is 500 mg/m<sup>2</sup> on Day Three (maximum recommended dose of 1000 mg on the third day).

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Dexrazoxane has been in clinical use since the early 1970's and has been marketed as the product Zinecard, by Pfizer (formerly Pharmacia) for the indication of Prevention of cardiomyopathy associated with doxorubicin administration in the USA since 1995. Bedford supplies a Generic version of the drug and Chiron supplies the drug outside of the USA as Cardioxane.

Unresolved inspectional issues:

NDA was beset with several discrepancies and issues with the listing of manufacturing and testing sites and statements on their readiness for inspection. Two separate reminders were sent to the firm on March 1, 2006, and March 16, 2006 asking the firm to provide a statement regarding readiness for inspection of the listed sites. In an amendment dated March 17, 2006, the firm provided the following responses.

- The \_\_\_\_\_ manufacturer \_\_\_\_\_ would be ready for inspection in 3 months. (Subsequently this site was inspected and deemed acceptable for cGMP compliance.)
- The \_\_\_\_\_ manufacturer \_\_\_\_\_ and the testing sites \_\_\_\_\_ Integrated Commercialization Solutions, USA were all listed as being ready for inspection.
- The \_\_\_\_\_ manufacturer Hameln, Pharma., GmbH, Germany and the \_\_\_\_\_ site Integrated Commercialization Solutions (ICS), USA were also listed as being ready for inspections.
- The inspection readiness statement on the subcontractor to \_\_\_\_\_ that carries out testing \_\_\_\_\_ was pending. However, an amendment dated March 31, 2006 clarified that this facility would not be ready for inspections until January, 2007.

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The District Office recommended "withhold" for Integrated Commercialization Solutions, USA on May 4, 2006 since the firm was not ready for inspections despite a statement of readiness dated March 17, 2006. Subsequently, in an e-mail dated July 19, 2006, the firm indicated that the ICS facility was now ready for inspections, however, the firm was asked to submit a formal amendment to this effect. Meanwhile, the EES recommendation was changed from "WH" to "PN" for this facility.

To date, \_\_\_\_\_ ICS are listed with "PN" status in the EES. The inspections of the first three sites, which are foreign sites, have been scheduled since April 3, 2006 and that for the ICS has been assigned on July 20, 2006. Also, as indicated above, \_\_\_\_\_ that carries out \_\_\_\_\_ testing \_\_\_\_\_ will not be ready until January, 2007. Therefore, it is unlikely that complete compliance action could be taken within the PDUFA date of August 1, 2006. Hence, overall compliance recommendation in this review cycle will not impact our "AE" recommendation for this NDA.

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Unresolved issues in applicant's e-mail dated July 19, 2006:

As indicated above, the firm has not submitted an official amendment indicating that ICS facility is ready for inspections. Additionally, issues on chemistry documents of validation methods not using USP methods have not been resolved. The e-mail response indicates that all methods have been changed to refer to current USP. The firm stated that since the changes were merely in validation methods and were not substantive, it would be cumbersome to re-submit all the documents at this late stage in the review cycle. Therefore, the firm proposed that the Agency accept some kind of blanket assurance that all methods are now USP and that the corrected documents would then be re-submitted after the action date of August 1, 2006.

This approach is unacceptable. It is expected that all revised CMC documents of validation methods be submitted and be reviewed and accepted before an NDA can be approved.

Unresolved issues with microbial product quality:

The microbiology reviewer, Ansthasia Lolas in her review dated July 12, 2006 recommended "AE" action pending resolution of microbiology deficiencies, namely incomplete studies on product-specific filter bacterial retention for the lyophilized product and inconsistencies and inadequate data submitted in support of the sterilization of the solvent. The reviewer opined that the risk to the patient is high because without adequate sterilization validation data, the sterility of the product is not assured.

b(4)

Overall recommendation:

In view of the above discussion, the NDA is approvable from CMC perspective. The applicant should fully resolve and address the above deficiencies before the NDA can be approved.

List of CMC deficiencies (including microbiology deficiencies taken from microbiology review):

1. Your amendment dated March 31, 2006 states that \_\_\_\_\_ would not be ready for inspections until January, 2007. Since this facility carries out testing of the \_\_\_\_\_ and since this function is critical to the assurance of product quality, the facility is required to be inspected before approval of the NDA. Therefore, in your resubmission, provide a statement of readiness of this facility for inspections.

b(4)

2. Your amendment dated March 17, 2006 stated that Integrated Commercialization Solutions, USA (ICS) was ready for inspections. However, as on May 4, 2006, this facility was not ready for inspections. Your subsequent e-mail correspondence dated July 19, 2006 suggested that ICS was now ready for inspections, however, an official amendment stating readiness of this firm for inspection was not submitted. In your resubmission provide a statement of readiness of this facility for inspections.

b(4)

4. In your e-mail correspondence dated July 19, 2006, you proposed that the Agency accept a blanket assurance from you that all analytical methods are now USP compliant and that the corrected validation and related documents would be re-submitted post-approval. This approach is not acceptable. Provide a clear documentation of revised analytical methods and data on their validations in your resubmission.
5. Regarding the microbiological environmental monitoring program, provide the growth media, incubation conditions, and actions taken when alert and action levels are exceeded. Identify the air samplers used.
6. The product-specific bacterial filter retention study should be submitted as soon as it is complete along with the flow rate and pressure parameters used during production.
7. \_\_\_\_\_ has 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.
8. The amended NDA response indicates that for the production temperature set-point for the sterilization of the solvent is \_\_\_\_\_. However, the container-closure integrity test data provided are valid for a temperature set-point of \_\_\_\_\_. The inconsistencies regarding the temperature set-point of the sterilization cycle should be resolved with additional clarifications.

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9. \_\_\_\_\_

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/s/

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Ravi Harapanhalli  
7/24/2006 06:16:27 PM  
CHEMIST

**Initial Quality assessment  
Branch V**

**Pre-marketing Assessment and Manufacturing Science Division III  
Office of New Drug Quality Assessment**

OND Division: Division of Oncology Drug Products  
NDA: 22-025  
Applicant: Topo Target A/S  
Stamp Date: 1-Feb-06  
PDUFA Date: 1-Dec-06  
Proposed Trade Name: Totect™  
Established Name: Dexrazoxane  
Laboratory Code:  
Dosage Form: Lyophilized powder for Injection  
Route of Administration: Intravenous infusion  
Indication: Treatment of anthracycline extravasation during chemotherapy  
  
CMC Reviewer: Yung-Ao Hsieh, Ph. D.

	Yes	No
ONDQA Fileability:	<u>√</u>	
Draft Comments for 74-day Letter:	<u>√</u>	

## Summaries, Critical Issues and Comments

### A. SUMMARIES

#### Background Summary

NDA 22-025 has been submitted for Totect (dexrazoxane hydrochloride) for Injection, indicated for the treatment of extravasation occurring during anthracycline chemotherapy. Dexrazoxane has been in clinical use since the early 1970's and is marketed under the trade name of ZINECARD (for injection) by Pharmacia & Upjohn Company, a division of Pfizer Inc. It is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer [20 and 500 mg lyophilizate, see Zinecard package insert (October 2004)]. A generic version of this drug (Dexrazoxane) is available from Bedford. This drug is also available as Cardioxane outside of the US. Cardioxane is manufactured by Chiron using a different process, but has specifications similar to those of Zinecard.

On 14-Nov-05, the applicant inquired if the Agency would review this NDA with only 3 months stability data for the drug diluent and was informed that this would be acceptable. The applicant plans to provide stability updates for the drug diluent during the course of NDA review. This NDA is filed under Section 505(b)(2) of the Food, Drug and Cosmetic Law and has been granted orphan drug status by the Agency on 25-Mar-04. The applicant is requesting Priority Review for this application. All official meeting minutes are filed under IND 70,774

The applicant, TopoTarget (Copenhagen, Denmark) has transferred the responsibilities of US agent for this NDA to Alba Biopharm Advisors, Inc in Raleigh, NC. Alba Biopharm will be responsible for all communication to and from the Agency.

#### Drug Substance Summary

Dexrazoxane is a bisdioxopiperazine (see Figure 1) that readily enters cells and acts as a chelating agent and a catalytic inhibitor of DNA topoisomerase II. The chemical name is 2,6-piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis-, (S) or (S)-(+)-1,2-bis(3,5-dioxopiperazin-1-yl)propane. Its physicochemical properties are tabulated in Table 1 on next page.

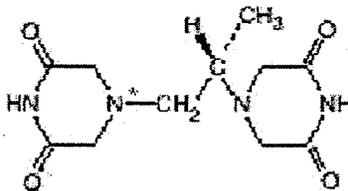


Figure 1. Chemical Structure of Dexrazoxane

Appearance	A white to off-white powder
Molecular Formula	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub>
Molecular Weight	268.3
Melting Point	194 ± 3°C
Solubility	soluble in dioxins and .1 N HCl; sparingly soluble in water, THF, pH 4.0, 7.0 and 9 buffers

**Table 1. Physicochemical Properties of Dexrazoxane**

[Redacted text block containing multiple lines of obscured information]

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Dexrazoxane has been in clinical use since the early 1970's. It is obtained by chemical synthesis starting from the commercially available 1,2-diaminopropane-N,N,N'-tetracaetic acid which provided the backbone of the drug substance molecule.

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\_\_\_\_\_

The NDA provided 3 batches of batch analysis data; all of the specified impurities have been identified. The manufacturing process of the drug substance appeared to be adequately controlled.

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### Drug Product Summary

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ The reconstituted solution should be diluted with 0.9% NaCl solution prior to administration.

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\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Dexrazoxane can undergo hydrolysis; the drug product is formulated as a lyophile.

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\_\_\_\_\_ Additionally, stability data of 15 batches of dexrazoxane powder for storage at 25°C (non-ICH) for at least 3 years were also provided in the application. The applicant is requesting a \_\_\_\_\_ shelf life for the dexrazoxane lyophilized powder. The reconstituted dexrazoxane solution is stable for at least 4 h after reconstitution and subsequent dilution.

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The reconstitution solvent is a sterile 50% sodium lactate solution packaged in colorless neutral 50 mL glass vials. \_\_\_\_\_

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\_\_\_\_\_ Stability data for 3 month are available. The Division has agreed to accept limited stability data and accept stability updates during the course of NDA review.

**B. CRITICAL ISSUES FOR REVIEW AND RECOMMENDATION:**

**Drug Substance**

Dexrazoxane is not an NME. The synthesis of the drug substance involves a \_\_\_\_\_

\_\_\_\_\_ The optical purity of the starting material is well-controlled.

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\_\_\_\_\_ The manufacturing process yields dexrazoxane of consistent quality and purity as demonstrated by the batch analysis data provided.

**Drug Product**

1. The clinical efficacy studies performed to support this application utilized commercial preparation of dexrazoxane, i.e., Zinecard and Cardioxane. Similar to Zinecard, the proposed new drug product pack contains a dexrazoxane lyophilizate vial and a Sodium Lactate Injection vial. \_\_\_\_\_

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2. Dexrazoxane degrades rapidly in aq. medium with pH > 7. It is more stable in 0.1 N HCl (93% remained after 4 days) and 0.01 N HCl (100%, after 8 h). The degradation rate is also temperature-dependent.

3. \_\_\_\_\_

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4. The identified critical manufacturing steps are: \_\_\_\_\_

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5. A suitable lyophilizing cycle has been developed. \_\_\_\_\_

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6. The supplied sodium lactate diluent is equivalent to Sodium Lactate Injection,

USP.

7. The manufacturing processes for the dexrazoxane powder and sodium lactate reconstitution solution appeared to be adequately controlled.
8. The NDA was submitted with limited reconstitution solvent stability data. The Division has agreed to accept limited stability data and accept stability updates during the course of NDA review.

**C. COMMENTS FOR 74-DAY LETTER:**

Stability updates for the reconstitution solvent should be submitted for review as soon as possible.

**D. RECOMMENDATION FOR FILEABILITY: Fileable (see Fileability Template)**

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?		√	
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Additional data for the reconstitution solvent should be provided in a timely update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?		√	Methods validation data are included. The MV package will be submitted post-approval.
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)		√ √	Microbiology <b>Pharm/Tox</b>

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/s/

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Ravi Harapanhalli  
4/19/2006 03:03:55 PM  
CHEMIST

Placing the IQA review of Yung Ao Hsieh into  
the DFS on his behalf,