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RESEARCH**

APPLICATION NUMBER:

22-025

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: Totect™

Generic name: Dexrazoxane

Type of dosage form and strength(s): Powder and Solvent for Injection

Indication(s): the Applicant's proposed indication is, "Totect™ is indicated for the treatment of anthracycline extravasation during chemotherapy."

NDA number, type: NDA 22-025, 1P

Applicant name: TopoTarget A/S

Submission date (letter date): 22-November-2006 N 000 AZ

OCPB Division name: Division of Pharmaceutical Evaluation I

OND: Division name: Division of Oncology Drug Products

OCPB Reviewer name: Gene M. Williams, Ph.D.

OCPB Team Leader name: N.A.M. Rahman, Ph.D.

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1. Executive Summary

A single commitment for clinical pharmacology and biopharmaceutics is recommended.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

The Applicant should commit to completing and submitting to the FDA the population pharmacokinetic analysis they 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.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dexrazoxane, the active ingredient in Totect, is the active ingredient in the approved drug Zinecard and is also available as a generic drug. All three formulations (Totect, Zinecard, and the generic) are lyophilizate powders that are reconstituted into simple solutions.

An NDA for Totect, with the same clinical and clinical pharmacology information as the current application, was judged "approvable" by the FDA in August of 2006. The clinical pharmacology and biopharmaceutics portion of that NDA was judged "acceptable" from the clinical pharmacology and biopharmaceutics perspective. Our review of that NDA is attached to this review as **Appendix 4.1**.

The Applicant has previously submitted a protocol to perform a study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation. The Applicant submitted a preliminary analysis of the data collected under that protocol to their IND during the current NDA review cycle. Our review of that IND submission is attached to this NDA review (**Appendix 4.2**).

2. Question-Based Review

An NDA for Totect, with the same clinical and clinical pharmacology information as the current application, was judged "approvable" by the FDA in August of 2006. The clinical pharmacology and biopharmaceutics portion of that NDA was judged "acceptable" from the clinical pharmacology and biopharmaceutics perspective. Our review of that NDA is attached to this review as **Appendix 4.1**.

3. De tailed Labeling Recommendations

Our prior review of the prior NDA includes labeling recommendations and is attached to this review as **Appendix 4.1**.

4. Appendi ces

4.1 Prior review of NDA 22-025

4.2 Review of the submission of December 4, 2006, IND 70,774 (Serial Number 004)

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Appendix 4.1 Prior review of NDA 22-025

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Clinical Pharmacology and Biopharmaceutics NDA Review

NDA number, type: NDA 22-025, 1P
Submission date (letter date): 16-MAR-2006 N 000
31-JAN-2006 N 000 BZ
Brand name: Totect™
Generic name: Dexrazoxane
Type of dosage form and strength(s): vials of 500 mg dexrazoxane as hydrochloride and vials of solvent for injection
Indication(s): the Applicant's proposed indication is, "Totect™ is indicated for the treatment of anthracycline extravasation during chemotherapy."
Applicant name: TopoTarget A/S
OCPB Division name: Division of Clinical Pharmacology V
OND: Division name: Division of Drug Oncology Products
OCPB Reviewer name: Gene M. Williams, Ph.D.
OCPB Team Leader name: Brian P. Booth, Ph.D.

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IC. 1.1.1

1. Executive Summary

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

We recommend a Phase 4 commitment to complete and submit to the FDA the Applicant's planned study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dexrazoxane, the active ingredient in Totect, is also the active ingredient in the approved drug Zinecard and is available as a generic drug. All three formulations (Totect, Zinecard, and the generic) are lyophilizate powders that are reconstituted into simple solutions.

No pharmacokinetics data was collected during the development of Totect. The Applicant has previously submitted a protocol to perform a study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

The NDA includes a literature survey of the pharmacokinetics that follow dosing of dexrazoxane at doses that approximate the package insert dose for Totect. These data suggest that the pharmacokinetics of dexrazoxane are not dose-dependent.

2. Question-Based Review

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Dexrazoxane, the active ingredient in Totect, is the active ingredient in the approved drug Zinecard and is also available as a generic drug. Dexrazoxane has been in clinical use since 1981 and Zinecard and generic dexrazoxane are currently approved "for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy."

The treatment of extravasation due to cytotoxic drug administration has been given Orphan Drug status.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The Applicant proposes that dexrazoxane has two major mechanisms of action: 1. chelation of iron through its ring-opened metabolite which reduces the iron-dependent free radical oxidative stress associated with anthracycline-induced cardiotoxicity, and 2. inhibition of topoisomerase II. It is not known to what extent each of these mechanisms contributes to the protective effect in anthracycline extravasation.

2.1.1. What are the proposed dosage(s) and route(s) of administration?

The below (indent, font change) is reproduced from the proposed package insert:

Totect™ must be administered under the supervision of a physician experienced in the oncology field.

Totect™ should be given once daily for 3 consecutive days.

The recommended dose is:

Day one: 1000 mg/m²

Day two: 1000 mg/m²

Day three: 500 mg/m²

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_____ the actual maximal dose is 5000 mg (Day 1: 2000 mg + Day 2: 2000 mg + Day 3: 1000 mg). The package insert will be modified to clarify the actual maximal dose.

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2.2. General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology studies were performed in the NDA.

The Applicant has studied Totect in a single course (of three days duration) in two similar, small, open-label, single-arm studies in patients suspected of experiencing anthracycline extravasation during chemotherapy infusions for malignancy. Both trials used a three day IV treatment regimen of Totect 1000 mg/m² commencing within 6 hours of a suspected event, a second Totect dose of 1000 mg/m² given 24 hours later, then 500 mg/m² given on the third day. The duration of infusion was 1 – 2 hours.

According to the Applicant, anthracycline extravasation usually leads to tissue necrosis requiring surgical excision and grafting. In the first study, TT01, 25 patients were

enrolled and 18 were judged evaluable for efficacy by the applicant. Upon finding no treatment failures with Totect therapy (i.e. no surgical resections needed) in the 18 evaluable patients in Denmark, the applicant then conducted study TT02 in an additional population of patients in Europe using the same eligibility and Totect therapy. The results in TT02 were very similar, with only one evaluable patient (1/36) requiring surgical repair of anthracycline tissue injury. These two studies comprise the NDA for Totect, along with nonclinical studies in rodents in support of the Applicant's claims.

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

Neither a thorough QTc study nor a pilot study designed to assess any effects of dexrazoxane on QT-interval were performed.

A search for the letters "qt" in the Zinecard package insert shows no occurrences.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The choice of a tolerable dose for the 3-day schedule was based on the published literature on Phase 1 and 2 trials and the principle of administering as high a dose as possible.

While the optimal dose has not been determined, there are no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The following (FDA Table 1.) is reproduced from the current Zinecard package insert.

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FDA Table 1. CLINICAL PHARMACOLOGY Pharmacokinetics section of the Zinecard package insert

Pharmacokinetics: The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin. The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of ZINECARD administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.

SUMMARY OF MEAN (%CV^a) DEXRAZOXANE
PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF
10:1 OF ZINECARD: DOXORUBICIN

Dose Doxorubicin (mg/m ²)	Dose Zinecard (mg/m ²)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m ²)	Renal Clearance (L/h/m ²)	bVolume of Distribution (L/m ²)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

a Coefficient of variation

b Steady-state volume of distribution

Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with ZINECARD have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.

Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of ZINECARD was excreted in the urine.

Protein Binding: *In vitro* studies have shown that ZINECARD is not bound to plasma proteins.

The NDA includes a literature survey of published trials where dexrazoxane pharmacokinetics were determined (Table 2.7.2-2, page 4 of the Clinical Pharmacology Summary). The Reviewer has used this table, together with the Zinecard package insert, to create **FDA Table 2.** (following page). The lower portion of the table contains the literature information and is sorted by the Rate of Infusion. With the possible exception of the highest infusion rate studied (Schroeder et al., 2003), there is no apparent change in pharmacokinetics as a function of dose or infusion rate. Schroeder et al. (2003) used a dose 1.5-fold greater than that recommended for Totect and an infusion rate 6-fold greater than that recommended for Totect.

FDA Table 2. Literature Values for Dexrazoxane Pharmacokinetics							
Source	Zinecard Dose	Duration of Infusion	Rate of Infusion	Concomittant Chemotherapy	Elimination Half-Life	Plasma Clearance	Volume of Distribution
	(mg/m ²)	(h)	(mg/m ² /h)		(h)	(L/h/m ²)	(L/m ²)
Proposed Totect Package Insert	1000	1 - 2	500 - 1000	Antracyclines	PK Not Performed	PK Not Performed	PK Not Performed
Zinecard Package Insert	500	0.25	2000	Doxorubicin	2.5	7.9	22
Zinecard Package Insert	600	0.25	2400	Doxorubicin	2.1	6.2	22
Tetef et al	(125 - 250) Daily X 4	96	2.6	None	2	7.2	Not Reported
Earhart et al., 1982	1000	48	20.8	None	2.9	8.8	10.3
Earhart et al., 1982	1000	8	125	None	2.4	7.4	5.4
Hochster et al., 1992	60 - 900	0.25	240 - 3600	Doxorubicin	4.2	6.7	Not Reported
Earhart et al., 1982	1000	0.5	2000	None	2	9.4	7.8
Holcenberg et al., 1986	(3000 - 4000) Daily X 3	2	1500 - 2000	None	1.9	11.1	39.5
Jakobsen et al., 1994	600 - 1000	0.25	2400 - 4000	Epirubicin + 5-Fluoro-Uracil + Cyclophosphamide + Tamoxifen	2.6	8.0	20.2
Vogel et al., 1987	(3800 - 7400) Once Weekly	1	3800 - 7400	None	3.2	11.9	53.5
Rosing et al., 1999	1000	0.25	4000	Doxorubicin + 5-Fluoro-Uracil + Cyclophosphamide	2.9	8.3	24.7
Schroeder et al., 2003	1500	0.25	6000	Etoposide + Methylprednisolone	9.1	13.3	Not Reported

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The following (FDA Table 3.) is reproduced from the current Zinecard package insert.

FDA Table 3. CLINICAL PHARMACOLOGY Special Populations section of the Zinecard package insert

Special Populations:

Pediatric: The pharmacokinetics of ZINECARD have not been evaluated in pediatric patients.

Gender: Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 mL/min/m² versus 133 mL/min/m²). This gender effect is not clinically relevant

Renal insufficiency: The pharmacokinetics of ZINECARD were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Hepatic insufficiency: The pharmacokinetics of ZINECARD have not been evaluated in patients with hepatic impairment. The ZINECARD dose is dependent upon the dose of doxorubicin (see **DOSAGE AND ADMINISTRATION**). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment

There are noteworthy differences between the Zinecard package insert and the proposed Totect package insert in the recommendations for dosing in patients with renal impairment. The Zinecard package insert recommends that dose be reduced by 50% in patients with creatinine clearance < 40 mL. The proposed Totect package insert

The concentration-toxicity (hematologic toxicity as well as other toxicities) relationship for dexrazoxane is unknown. As the concentration-toxicity relationship is unknown, the Reviewer recommends that the package insert recommend that dosing be adjusted for patients with renal impairment. The quantitative basis for the adjustment comes from the Zinecard supplement reviewed by the FDA in 2005. A portion of the Executive Summary from this review is reproduced below (indent, font change).

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This study examined the pharmacokinetics (PK) of dexrazoxane following a brief intravenous (IV) infusion of 150-mg/m² dexrazoxane in otherwise healthy male and female subjects with varying degrees of renal function. Results indicated that dexrazoxane clearance was reduced in subjects with renal impairment resulting in a 2-fold increase in AUC in subjects with moderate (CLCR=30-50 ml/min) to severe (CLCR<30 ml/min). Calculations showed that a 50% reduction in dose (from 500 mg/m² to 250 mg/m²) in patients with CLCR values below 40 ml/min would result in exposures that would be equivalent to that in controls.

At the time of approval of Zinecard, the Applicant committed to performing a Phase 4 study in patients with hepatic impairment. Although this study was not completed, the FDA judged the commitment as "fulfilled" based upon the Applicant's argument that they could not enroll to the study and the package insert recommendation for constant ratio (10:1 dexrazoxane:anthracycline) dosing (FDA Table 3., above).

The proposed Totect package insert language regarding _____ is reproduced, below (indent, font change).

b(4)

The maximum tolerated dose (MTD) for dexrazoxane administered over 3 or fewer consecutive days has been estimated at 3000 – 10500 mg/m² (total dose across the 3 day period; Table 2.7.2-4, page 14 of the Clinical Pharmacology Summary). The recommended Totect dose is 2500 mg/m², capped at a maximum dose of 5000 mg (the

b(4)

_____ Based on the MTD data, and the patient population for the extravasation indication, we are not recommending a dose reduction for extravasation patients with hepatic impairment.

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2.4. Extrinsic Factors

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The following (FDA Table 3.) is reproduced from the current Zinecard package insert.

FDA Table 3. CLINICAL PHARMACOLOGY Drug Interactions section of the Zinecard package insert

Drug Interactions: There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol; in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.

2.5 *General Biopharmaceutics*

Totect is a lyophilizate powder that is reconstituted in _____ouffer to from a simple solution for intravenous injection. There are no biopharmaceutics issues.

b(4)

2.6 *Analytical Section*

No pharmacokinetics were performed for the NDA.

3 *Detailed Labeling Recommendations*

The Applicant's proposed package insert (Appendix 4.1) was developed from literature data. However, as evidenced by dexrazoxane being available as a generic drug, the package insert for Zinecard is not proprietary and can be used to craft a package insert for Totect. The Reviewer has taken the approach of using the approved Zinecard package insert as a starting point for the package insert. **FDA Table 4.** is the current Zinecard package insert together with the Reviewer's recommended revisions.

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>CLINICAL PHARMACOLOGY</p> <p>Mechanism of Action: The mechanism by which ZINECARD exerts its cardioprotective activity is not fully understood. Dexrazoxane is a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring-opened chelating agent that interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline induced cardiomyopathy.</p> <p>Pharmacokinetics:</p> <p>The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin.</p>	<p>CLINICAL PHARMACOLOGY</p> <p>Mechanism of Action: <i>To be reviewed by the FDA Pharm/Tox Reviewer</i></p> <p>Pharmacokinetics:</p> <p>The pharmacokinetics of dexrazoxane following dosing to patients with extravasation have not been studied.</p> <p>The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin. The disposition kinetics of</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of ZINECARD administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.</p>	<p>The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of dexraoxane administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.</p> <p><i>[No changes to Table]</i></p>

SUMMARY OF MEAN (%CV^a) DEXRAZOXANE PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF 10:1 OF ZINECARD: DOXORUBICIN

Dose Doxorubicin (mg/m ²)	Dose Zinecard (mg/m ²)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m ²)	Renal Clearance (L/h/m ²)	bVolume of Distribution (L/m ²)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

a Coefficient of variation

b Steady-state volume of distribution

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with ZINECARD have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.</p> <p>Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of ZINECARD was excreted in the urine.</p> <p>Protein Binding: <i>In vitro</i> studies have shown that ZINECARD is not bound to plasma proteins.</p>	<p>Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with dexrazoxane have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.</p> <p>Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of dexrazoxane was excreted in the urine.</p> <p>Protein Binding: <i>In vitro</i> studies have shown that dexrazoxane is not bound to plasma proteins.</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Special Populations:</p> <p>Pediatric: The pharmacokinetics of ZINECARD have not been evaluated in pediatric patients.</p> <p>Gender: Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 mL/min/m² versus 133 mL/min/m²). This gender effect is not clinically relevant.</p> <p>Renal insufficiency: The pharmacokinetics of ZINECARD were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).</p>	<p>Special Populations:</p> <p>Pediatric: The pharmacokinetics of dexrazoxane have not been evaluated in pediatric patients.</p> <p>Gender: There are no clinically relevant differences in the pharmacokinetics of dexrazoxane between males and females.</p> <p>Renal insufficiency: The pharmacokinetics of dexrazoxane were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Hepatic insufficiency: The pharmacokinetics of ZINECARD have not been evaluated in patients with hepatic impairment. The ZINECARD dose is dependent upon the dose of doxorubicin (see DOSAGE AND ADMINISTRATION). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment.</p> <p>Drug Interactions: There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.</p> <p>PRECAUTIONS Patients with Moderate or Severe Renal Insufficiency Greater exposure to dexrazoxane may occur in patients with compromised renal function. The ZINECARD dose should be reduced by 50% in patients with creatinine clearance values <40 mL/min (see DOSAGE AND ADMINISTRATION).</p>	<p>Hepatic insufficiency: The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic impairment.</p> <p>Drug Interactions: There were no significant changes in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.</p> <p>PRECAUTIONS Patients with Moderate or Severe Renal Insufficiency Greater exposure to dexrazoxane may occur in patients with compromised renal function. The Totect dose should be reduced by 50% in patients with creatinine clearance values <40 mL/min (see DOSAGE AND ADMINISTRATION).</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
Drug Interactions ZINECARD does not influence the pharmacokinetics of doxorubicin.	Drug Interactions ZINECARD does not influence the pharmacokinetics of doxorubicin.

FDA Table 5. is the **PRECAUTIONS General** and **DOSAGE and ADMINISTRATION** portions of the proposed Totect package insert, as these portions of the Totect package insert cannot be taken from the Zinecard package insert.

4 *Appendices*

- 4.1 Package insert (Applicant's proposed)
- 4.2 Current Zinecard Package insert
- 4.3 Cover sheet and OCPB filing/review form

25 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Appendix 4.3 Cover sheet and OCPB filing/review form

APPEARS THIS WAY ON ORIGINAL

I. *Office of Clinical Pharmacology and Biopharmaceutics*
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-025	Brand Name	Totect™
OCPB Division	V	Generic Name	dexrazoxane
Medical Division	Oncology	Drug Class	None
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	for the treatment of anthracycline extravasation during chemotherapy
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	Powder for reconstitution and solvent for injection
		Dosing Regimen	Day 1: 1000 mg/m ² daily X2 Day 2: 1000 mg/m ² Day 3: 500 mg/m ² Each dose as a 1 – 2 h infusion
Date of Submission	January 31, 2006	Route of Administration	IV
Estimated Due Date of OCPB Review		Sponsor	TOPOTARGET A/S
PDUFA Due Date	August 1, 2006	Priority Classification	1P
Division Due Date	July 25, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>II. Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
	Phase 2:			
	Phase 3:			
PK/PD:				
	Phase 1 and/or 2, proof of concept:			
	Phase 3 clinical trial:			
Population Analyses -				
	Data rich:			
	Data sparse:			
II. Biopharmaceutics				
	Absolute bioavailability:			
	Relative bioavailability -			
	solution as reference:			
	alternate formulation as reference:			
	Bioequivalence studies -			
	traditional design; single / multi dose:			
	replicate design; single / multi dose:			
	Food-drug interaction studies:			
	In-Vitro Release BE			
	(IVIVC):			
	Bio-wavier request based on BCS			
	BCS class			
III. Other CPB Studies				
	Genotype/phenotype studies:			
	Chronopharmacokinetics			
	Pediatric development plan			
	Literature References	X	8	8
	Total Number of Studies		0	0
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	No			
QBR questions (key issues to be considered)	Dosing of patients with renal impairment			
Other comments or information not included above	Dexrazoxane is approved as Zinecard and as a a generic. The NDA contains no new data – only literature references and discussion are provided			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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/s/

Gene Williams
7/20/2006 05:31:19 PM
BIOPHARMACEUTICS

Brian Booth
7/24/2006 11:23:16 AM
BIOPHARMACEUTICS

Atiqur Rahman
7/24/2006 12:19:30 PM
BIOPHARMACEUTICS

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**Appendix 4.2 Review of the submission of
December 4, 2006, IND 70,774 (Serial Number 004)**

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Fomal/Informal Consults								
From: Gene M. Williams, Ph.D.		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission								
DATE: 26-Mar-07	IND No.: 70,774 Serial No.: 004	NDA No.	DATE OF DOCUMENT	4-Dec-06						
NAME OF DRUG Totect (dexrazoxane)		PRIORITY CONSIDERATION	Date of informal/Formal Consult:							
NAME OF THE SPONSOR: TopoTarget A/S										
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE										
<table style="width:100%; border: none;"> <tr> <td style="width:33%; vertical-align: top;"> <input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input checked="" type="checkbox"/> PHASE IV RELATED </td> <td style="width:33%; vertical-align: top;"> <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) </td> <td style="width:33%; vertical-align: top;"> <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): </td> </tr> </table>					<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input checked="" type="checkbox"/> PHASE IV RELATED	<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):			
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REVIEW ACTION										
<table style="width:100%; border: none;"> <tr> <td style="width:33%; vertical-align: top;"> <input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail) </td> <td style="width:33%; vertical-align: top;"> <input type="checkbox"/> Oral communication with Name: [] </td> <td style="width:33%; vertical-align: top;"> <input checked="" type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): [] </td> </tr> <tr> <td colspan="3" style="border: none;"> <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: [] </td> </tr> </table>					<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)	<input type="checkbox"/> Oral communication with Name: []	<input checked="" type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): []	<input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []		
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)	<input type="checkbox"/> Oral communication with Name: []	<input checked="" type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): []								
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REVIEW COMMENT(S)										
<input checked="" type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR										
COMMENTS/SPECIAL INSTRUCTIONS: <div style="text-align: center;"> </div>										
SIGNATURE OF REVIEWER: <u>Gene M. Williams, Ph.D.</u>			Date <u>27-Mar-07</u> Date _____							
SIGNATURE OF TEAM LEADER: <u>Brian P. Booth, Ph.D.</u>										
CC.: TL: [BBooth]; DDD: [ARahman]			Project Manager: <u>Brenda Atkins</u> Date _____							

Background

Totect (dexrazoxane 500 mg powder and solvent for injection) for use in patients suspected of having extravasation from anthracycline dosing, was the topic of a recent NDA (NDA 22-025) which was judged approvable by the FDA. The NDA was judged acceptable from the clinical pharmacology perspective, with a recommendation that, should the NDA be approved, the following Phase 4 commitment should be included in the approval (indent, font change).

We recommend a Phase 4 commitment to complete and submit to the FDA the Applicant's planned study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

The recommended regimen for use in extravasation is 3 doses given 24 hours apart: 1000 mg/m² on Day 1, 1000 mg/m² on Day 2 and 500 mg/m² on Day 3. The 1000 mg/m² doses exceed the doses of dexrazoxane which are used for the approved indication of reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration. For the approved indication, dexrazoxane is given at a fixed ratio based on the doxorubicin dose (the ratio of dexrazoxane to doxorubicin is 10:1).

NDA 22-025 did not include pharmacokinetics data from patients that received the clinical regimen. In response to FDA's concern over the lack of pharmacokinetics data, the Applicant designed Protocol TT04. Among the comments FDA forwarded regarding Protocol TT04 were the following.

2. We recommend that the sample size be 15. In the absence of a control group, the ability of even 15 patients to provide sufficient power to detect differences in the pharmacokinetics due to the high doses of dexrazoxane administered is limited. A sample size of 5 is inadequate.
4. We recommend that population pharmacokinetic modeling be used as the data analysis method. An attempt to model the relationship between concentration and clinical outcome (extravasation injury and clinical toxicity) should be made

The current submission includes pharmacokinetic results from the first 6 patients in Study TT04. A population analysis of these data, and an attempt to correlate concentrations with effect, is not included. The Applicant indicates that such an analysis will be performed for the final study report.

The sentences below are excerpted from the submission (indent, font change).

It can be seen that the results obtained for all 6 patients follow the model and are in agreement with the results published in the literature. Thus, half-lives are as expected and there is no indication of clinically significant changes in the drug disposition and no indication of drug accumulation over the three days.

We would therefore like to discuss with the FDA the need for further patients in this study. It is recognized that 15 patients is a minimum number for a regular *de novo* pharmacokinetic study. However, in this case there are already 6 published dexrazoxane pharmacokinetic reports (using various doses/schedules) in the literature and the homogenous results in the first six TT04 patients do not indicate any general differences from previous reports. The question, therefore, is whether it is ethically defensible to continue to accrue such acute patients for the purpose of pharmacokinetic sampling and whether the information available to date is sufficient.

Specific Questions from the Applicant

Question to the FDA: Based on the new information obtained from the first 6 patients, would the FDA agree that recruitment to the TT04 study could now be stopped? If the FDA has further concern about the sample size or needs further information, the applicant would be grateful for an opportunity to discuss this at a teleconference.

Recommendations to the Sponsor:

In order to make a final determination regarding whether the data from the 6 patients is sufficient, we would like to review a complete analysis. We recommend that you perform the population analysis you've agreed to and 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 data acquisition is needed.

Signatures

Gene Williams, Ph.D. Reviewer, DCP 5

Brian Booth, Ph.D., Team Leader, DCP 5

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/s/

Gene Williams
3/27/2007 02:59:41 PM
BIOPHARMACEUTICS

Brian Booth
3/27/2007 03:08:16 PM
BIOPHARMACEUTICS

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

/s/

Gene Williams
5/11/2007 03:44:08 PM
BIOPHARMACEUTICS

Atiqur Rahman
5/11/2007 04:45:18 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Submission/Date: IND 70,774 002 / 11-Oct-2004

Drug Name: Topotec[®] (dexrazoxane)

Dosage Form: powder for reconstitution and injection

Applicant: Alba Biopharm Advisors for TopoTarget A/S

Reviewer: Gene M. Williams, Ph.D.

Type of Submission: Meeting Package

Background

Dexrazoxane is marketed in the United States as ZINECARD (Pfizer) for the prevention of cardiomyopathy associated with doxorubicin administration, and outside the US as Cardioxane (Chiron).

The current IND is for the use of dexrazoxane “for treatment of extravasation occurring during anthracycline therapy.”

Both ZINECARD and Topotec[®] are supplied as sterile hydrochloride salts for reconstitution.

The dose regimen being recommended is 2500 mg/m² given over a three day period: treatment one = 1000 mg/m², administered within 6 hours of extravasation, as a 1-2 hour infusion
treatment two = 1000 mg/m², administered 24 hours after treatment 1, as a 1-2 hour infusion, and
treatment three = 500 mg/m² administered 48 hours after treatment 1, as a 1-2 hour infusion.

The ZINECARD package insert gives the half-life for dexrazoxane as 2.1 – 2.5 hours.

The recommended (package insert) dosage ratio of ZINECARD:doxorubicin is 10:1 (eg, 500 mg/m² ZINECARD:50 mg/m² doxorubicin). The ZINECARD package insert recommends that the dose be “...given by slow I.V. push or rapid drip intravenous infusion.” The current ADRIAMYCIN (Doxorubicin HCl) for Injection package insert states: “The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m² as a single intravenous injection administered at 21-day intervals. ... When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m².” Taken together, the current maximal recommended dose of dexrazoxane for a 1.74 m² person is 1305 mg given as a single rapid infusion once

b(4)

every three weeks. The Sponsor's dose for a _____ person is _____ given over three days.

The minutes to the November 9, 2004 meeting are attached. No clinical pharmacology or biopharmaceutics issues were discussed.

Recommendations to the Sponsor

No action is indicated.

Gene M, Williams, Ph. D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation I

Brian P. Booth, Ph.D.
Acting Team Leader, Oncology
Division of Pharmaceutical Evaluation I

cc: HFD-150/RKane, AFarrell
HFD-860/BBooth, ARahman, MMehta

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.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: _____
Ann Farrell, M.D.
Medical Team Leader

ATTACHMENTS: FDA Standard EOP2 Bullets (not discussed)

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.-#2Year	>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
11/17/04 04:04:06 PM

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/s/

Dotti Pease
11/19/04 11:26:00 AM

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

/s/

Gene Williams
1/5/05 10:48:55 AM
BIOPHARMACEUTICS

Brian Booth
1/5/05 03:29:19 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics NDA Review

NDA number, type: NDA 22-025, 1P
Submission date (letter date): 16-MAR-2006 N 000
31-JAN-2006 N 000 BZ
Brand name: Totect™
Generic name: Dexrazoxane
Type of dosage form and strength(s): vials of 500 mg dexrazoxane as hydrochloride and vials of solvent for injection
Indication(s): the Applicant's proposed indication is, "Totect™ is indicated for the treatment of anthracycline extravasation during chemotherapy."
Applicant name: TopoTarget A/S
OCPB Division name: Division of Clinical Pharmacology V
OND: Division name: Division of Drug Oncology Products
OCPB Reviewer name: Gene M. Williams, Ph.D.
OCPB Team Leader name: Brian P. Booth, Ph.D.

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1. Executive Summary

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

We recommend a Phase 4 commitment to complete and submit to the FDA the Applicant's planned study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dexrazoxane, the active ingredient in Totect, is also the active ingredient in the approved drug Zinecard and is available as a generic drug. All three formulations (Totect, Zinecard, and the generic) are lyophilizate powders that are reconstituted into simple solutions.

No pharmacokinetics data was collected during the development of Totect. The Applicant has previously submitted a protocol to perform a study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

The NDA includes a literature survey of the pharmacokinetics that follow dosing of dexrazoxane at doses that approximate the package insert dose for Totect. These data suggest that the pharmacokinetics of dexrazoxane are not dose-dependent.

2. Question-Based Review

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Dexrazoxane, the active ingredient in Totect, is the active ingredient in the approved drug Zinecard and is also available as a generic drug. Dexrazoxane has been in clinical use since 1981 and Zinecard and generic dexrazoxane are currently approved "for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy."

The treatment of extravasation due to cytotoxic drug administration has been given Orphan Drug status.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The Applicant proposes that dexrazoxane has two major mechanisms of action: 1. chelation of iron through its ring-opened metabolite which reduces the iron-dependent free radical oxidative stress associated with anthracycline-induced cardiotoxicity, and 2. inhibition of topoisomerase II. It is not known to what extent each of these mechanisms contributes to the protective effect in anthracycline extravasation.

2.1.1. What are the proposed dosage(s) and route(s) of administration?

The below (indent, font change) is reproduced from the proposed package insert:

Totect™ must be administered under the supervision of a physician experienced in the oncology field.

Totect™ should be given once daily for 3 consecutive days.

The recommended dose is:

Day one: 1000 mg/m²

Day two: 1000 mg/m²

Day three: 500 mg/m²

_____the actual maximal dose is 5000 mg (Day 1: 2000 mg + Day 2: 2000 mg + Day 3: 1000 mg). The package insert will be modified to clarify the actual maximal dose.

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2.2. General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology studies were performed in the NDA.

The Applicant has studied Totect in a single course (of three days duration) in two similar, small, open-label, single-arm studies in patients suspected of experiencing anthracycline extravasation during chemotherapy infusions for malignancy. Both trials used a three day IV treatment regimen of Totect 1000 mg/m² commencing within 6 hours of a suspected event, a second Totect dose of 1000 mg/m² given 24 hours later, then 500 mg/m² given on the third day. The duration of infusion was 1 – 2 hours.

According to the Applicant, anthracycline extravasation usually leads to tissue necrosis requiring surgical excision and grafting. In the first study, TT01, 25 patients were

enrolled and 18 were judged evaluable for efficacy by the applicant. Upon finding no treatment failures with Totect therapy (i.e. no surgical resections needed) in the 18 evaluable patients in Denmark, the applicant then conducted study TT02 in an additional population of patients in Europe using the same eligibility and Totect therapy. The results in TT02 were very similar, with only one evaluable patient (1/36) requiring surgical repair of anthracycline tissue injury. These two studies comprise the NDA for Totect, along with nonclinical studies in rodents in support of the Applicant's claims.

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

Neither a thorough QTc study nor a pilot study designed to assess any effects of dexrazoxane on QT-interval were performed.

A search for the letters "qt" in the Zinecard package insert shows no occurrences.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The choice of a tolerable dose for the 3-day schedule was based on the published literature on Phase 1 and 2 trials and the principle of administering as high a dose as possible.

While the optimal dose has not been determined, there are no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The following (FDA Table 1.) is reproduced from the current Zinecard package insert.

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FDA Table 1. CLINICAL PHARMAOLOGY Pharmacokinetics section of the Zinecard package insert

Pharmacokinetics: The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin. The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of ZINECARD administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.

SUMMARY OF MEAN (%CV^a) DEXRAZOXANE
PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF
10:1 OF ZINECARD: DOXORUBICIN

Dose Doxorubicin (mg/m ²)	Dose Zinecard (mg/m ²)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m ²)	Renal Clearance (L/h/m ²)	bVolume of Distribution (L/m ²)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

a Coefficient of variation

b Steady-state volume of distribution

Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with ZINECARD have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.

Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of ZINECARD was excreted in the urine.

Protein Binding: *In vitro* studies have shown that ZINECARD is not bound to plasma proteins.

The NDA includes a literature survey of published trials where dexrazoxane pharmacokinetics were determined (Table 2.7.2-2, page 4 of the Clinical Pharmacology Summary). The Reviewer has used this table, together with the Zinecard package insert, to create **FDA Table 2.** (following page). The lower portion of the table contains the literature information and is sorted by the Rate of Infusion. With the possible exception of the highest infusion rate studied (Schroeder et al., 2003), there is no apparent change in pharmacokinetics as a function of dose or infusion rate. Schroeder et al. (2003) used a dose 1.5-fold greater than that recommended for Totect and an infusion rate 6-fold greater than that recommended for Totect.

FDA Table 2. Literature Values for Dexrazoxane Pharmacokinetics							
Source	Zinecard Dose	Duration of Infusion	Rate of Infusion	Concomittant Chemotherapy	Elimination Half-Life	Plasma Clearance	Volume of Distribution
	(mg/m ²)	(h)	(mg/m ² /h)		(h)	(L/h/m ²)	(L/m ²)
Proposed Totect Package Insert	1000	1 - 2	500 - 1000	Antracyclines	PK Not Performed	PK Not Performed	PK Not Performed
Zinecard Package Insert	500	0.25	2000	Doxorubicin	2.5	7.9	22
Zinecard Package Insert	600	0.25	2400	Doxorubicin	2.1	6.2	22
Tetef et al	(125 - 250) Daily X 4	96	2.6	None	2	7.2	Not Reported
Earhart et al., 1982	1000	48	20.8	None	2.9	8.8	10.3
Earhart et al., 1982	1000	8	125	None	2.4	7.4	5.4
Hochster et al., 1992	60 - 900	0.25	240 - 3600	Doxorubicin	4.2	6.7	Not Reported
Earhart et al., 1982	1000	0.5	2000	None	2	9.4	7.8
Holcenberg et al., 1986	(3000 - 4000) Daily X 3	2	1500 - 2000	None	1.9	11.1	39.5
Jakobsen et al., 1994	600 - 1000	0.25	2400 - 4000	Epirubicin + 5-Fluoro-Uracil + Cyclophosphamide + Tamoxifen	2.6	8.0	20.2
Vogel et al., 1987	(3800 - 7400) Once Weekly	1	3800 - 7400	None	3.2	11.9	53.5
Rosing et al., 1999	1000	0.25	4000	Doxorubicin + 5-Fluoro-Uracil + Cyclophosphamide	2.9	8.3	24.7
Schroeder et al., 2003	1500	0.25	6000	Etoposide + Methylprednisolone	9.1	13.3	Not Reported

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The following (FDA Table 3.) is reproduced from the current Zinecard package insert.

FDA Table 3. CLINICAL PHARMACOLOGY Special Populations section of the Zinecard package insert

Special Populations:

Pediatric: The pharmacokinetics of ZINECARD have not been evaluated in pediatric patients.

Gender: Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 mL/min/m² versus 133 mL/min/m²). This gender effect is not clinically relevant

Renal insufficiency: The pharmacokinetics of ZINECARD were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Hepatic insufficiency: The pharmacokinetics of ZINECARD have not been evaluated in patients with hepatic impairment. The ZINECARD dose is dependent upon the dose of doxorubicin (see **DOSAGE AND ADMINISTRATION**). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment

There are noteworthy differences between the Zinecard package insert and the proposed Totect package insert in the recommendations for dosing in patients with renal impairment. The Zinecard package insert recommends that dose be reduced by 50% in patients with creatinine clearance < 40 mL. The proposed Totect package insert

_____ The concentration-toxicity (hematologic toxicity as well as other toxicities) relationship for dexrazoxane is unknown. As the concentration-toxicity relationship is unknown, the Reviewer recommends that the package insert recommend that dosing be adjusted for patients with renal impairment. The quantitative basis for the adjustment comes from the Zinecard supplement reviewed by the FDA in 2005. A portion of the Executive Summary from this review is reproduced below (indent, font change).

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This study examined the pharmacokinetics (PK) of dexrazoxane following a brief intravenous (IV) infusion of 150-mg/m² dexrazoxane in otherwise healthy male and female subjects with varying degrees of renal function. Results indicated that dexrazoxane clearance was reduced in subjects with renal impairment resulting in a 2-fold increase in AUC in subjects with moderate (CLCR=30-50 ml/min) to severe (CLCR<30 ml/min). Calculations showed that a 50% reduction in dose (from 500 mg/m² to 250 mg/m²) in patients with CLCR values below 40 ml/min would result in exposures that would be equivalent to that in controls.

At the time of approval of Zinecard, the Applicant committed to performing a Phase 4 study in patients with hepatic impairment. Although this study was not completed, the FDA judged the commitment as "fulfilled" based upon the Applicant's argument that they could not enroll to the study and the package insert recommendation for constant ratio (10:1 dexrazoxane:anthracycline) dosing (FDA Table 3., above).

The proposed Totect package insert language regarding _____ is reproduced, below (indent, font change).

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The maximum tolerated dose (MTD) for dexrazoxane administered over 3 or fewer consecutive days has been estimated at 3000 – 10500 mg/m² (total dose across the 3 day period; Table 2.7.2-4, page 14 of the Clinical Pharmacology Summary). The recommended Totect dose is 2500 mg/m², capped at a maximum dose of 5000 mg

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_____ Based on the MTD data, and the patient population for the extravasation indication, we are not recommending a dose reduction for extravasation patients with hepatic impairment.

2.4. Extrinsic Factors

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The following (FDA Table 3.) is reproduced from the current Zinecard package insert.

FDA Table 3. CLINICAL PHARMACOLOGY Drug Interactions section of the Zinecard package insert

Drug Interactions: There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.

2.5 *General Biopharmaceutics*

Totect is a lyophilizate powder that is reconstituted in _____ buffer to form a simple solution for intravenous injection. There are no biopharmaceutics issues.

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2.6 *Analytical Section*

No pharmacokinetics were performed for the NDA.

3 *Detailed Labeling Recommendations*

The Applicant's proposed package insert (Appendix 4.1) was developed from literature data. However, as evidenced by dexrazoxane being available as a generic drug, the package insert for Zinecard is not proprietary and can be used to craft a package insert for Totect. The Reviewer has taken the approach of using the approved Zinecard package insert as a starting point for the package insert. **FDA Table 4.** is the current Zinecard package insert together with the Reviewer's recommended revisions.

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>CLINICAL PHARMACOLOGY</p> <p>Mechanism of Action: The mechanism by which ZINECARD exerts its cardioprotective activity is not fully understood. Dexrazoxane is a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring-opened chelating agent that interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline induced cardiomyopathy.</p> <p>Pharmacokinetics:</p> <p>The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin.</p>	<p>CLINICAL PHARMACOLOGY</p> <p>Mechanism of Action: <i>To be reviewed by the FDA Pharm/Tox Reviewer</i></p> <p>Pharmacokinetics:</p> <p>The pharmacokinetics of dexrazoxane following dosing to patients with extravasation have not been studied.</p> <p>The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m² with 60 mg/m² of doxorubicin, and at a fixed dose of 500 mg/m² with 50 mg/m² doxorubicin. The disposition kinetics of</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of ZINECARD administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.</p>	<p>The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m². The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m² dose of dexraoxane administered 15 to 30 minutes prior to the 50 mg/m² doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.</p> <p><i>[No changes to Table]</i></p>

**SUMMARY OF MEAN (%CV^a) DEXRAZOXANE
PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF
10:1 OF ZINECARD: DOXORUBICIN**

Dose Doxorubicin (mg/m ²)	Dose Zinecard (mg/m ²)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m ²)	Renal Clearance (L/h/m ²)	bVolume of Distribution (L/m ²)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

a Coefficient of variation

b Steady-state volume of distribution

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with ZINECARD have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.</p> <p>Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of ZINECARD was excreted in the urine.</p> <p>Protein Binding: <i>In vitro</i> studies have shown that ZINECARD is not bound to plasma proteins.</p>	<p>Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m² dexrazoxane along with 50 mg/m² doxorubicin were 15.15 L/h/m² and 36.27 L/m², respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with dexrazoxane have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.</p> <p>Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m² dose of dexrazoxane was excreted in the urine.</p> <p>Protein Binding: <i>In vitro</i> studies have shown that dexrazoxane is not bound to plasma proteins.</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Special Populations:</p> <p>Pediatric: The pharmacokinetics of ZINECARD have not been evaluated in pediatric patients.</p> <p>Gender: Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 mL/min/m² versus 133 mL/min/m²). This gender effect is not clinically relevant.</p> <p>Renal insufficiency: The pharmacokinetics of ZINECARD were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).</p>	<p>Special Populations:</p> <p>Pediatric: The pharmacokinetics of dexrazoxane have not been evaluated in pediatric patients.</p> <p>Gender: There are no clinically relevant differences in the pharmacokinetics of dexrazoxane between males and females.</p> <p>Renal insufficiency: The pharmacokinetics of dexrazoxane were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC_{0-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min) (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
<p>Hepatic insufficiency: The pharmacokinetics of ZINECARD have not been evaluated in patients with hepatic impairment. The ZINECARD dose is dependent upon the dose of doxorubicin (see DOSAGE AND ADMINISTRATION). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment.</p> <p>Drug Interactions: There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.</p> <p>PRECAUTIONS Patients with Moderate or Severe Renal Insufficiency Greater exposure to dexrazoxane may occur in patients with compromised renal function. The ZINECARD dose should be reduced by 50% in patients with creatinine clearance values <40 mL/min (see DOSAGE AND ADMINISTRATION).</p>	<p>Hepatic insufficiency: The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic impairment.</p> <p>Drug Interactions: There were no significant changes in the pharmacokinetics of doxorubicin (50 mg/m²) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m²) in a crossover study in cancer patients.</p> <p>PRECAUTIONS Patients with Moderate or Severe Renal Insufficiency Greater exposure to dexrazoxane may occur in patients with compromised renal function. The Totect dose should be reduced by 50% in patients with creatinine clearance values <40 mL/min (see DOSAGE AND ADMINISTRATION).</p>

Continued:

FDA Table 4. Zinecard Package Insert and Reviewer's Recommended Totect Package Insert,

Zinecard Package Insert	OCP Reviewer's Recommended Totect Package Insert
Drug Interactions ZINECARD does not influence the pharmacokinetics of doxorubicin.	Drug Interactions ZINECARD does not influence the pharmacokinetics of doxorubicin.

FDA Table 5. is the **PRECAUTIONS General** and **DOSAGE and ADMINISTRATION** portions of the proposed Totect package insert, as these portions of the Totect package insert cannot be taken from the Zinecard package insert.

4 *Appendices*

- 4.1 Package insert (Applicant's proposed)
- 4.2 Current Zinecard Package insert
- 4.3 Cover sheet and OCPB filing/review form

25 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Appendix 4.3 Cover sheet and OCPB filing/review form

I. *Office of Clinical Pharmacology and Biopharmaceutics*
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-025	Brand Name	Totect™
OCPB Division	V	Generic Name	dexrazoxane
Medical Division	Oncology	Drug Class	None
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	for the treatment of anthracycline extravasation during chemotherapy
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	Powder for reconstitution and solvent for injection
		Dosing Regimen	Day 1: 1000 mg/2 daily X2 Day 2: 1000 mg/m2 Day 3: 500 mg/m2 Each dose as a 1 – 2 h infusion
Date of Submission	January 31, 2006	Route of Administration	IV
Estimated Due Date of OCPB Review		Sponsor	TOPOTARGET A/S
PDUFA Due Date	August 1, 2006	Priority Classification	1P
Division Due Date	July 25, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>II. Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	8	8	
Total Number of Studies		0	0	
Filability and QBR comments				
	"X" if yes	<u>Comments</u>		
Application filable?	x			
Comments sent to firm?	No			
QBR questions (key issues to be considered)	Dosing of patients with renal impairment			
Other comments or information not included above	Dexrazoxane is approved as Zinecard and as a generic. The NDA contains no new data – only literature references and discussion are provided			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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/

Gene Williams
7/20/2006 05:31:19 PM
BIOPHARMACEUTICS

Brian Booth
7/24/2006 11:23:16 AM
BIOPHARMACEUTICS

Atiqur Rahman
7/24/2006 12:19:30 PM
BIOPHARMACEUTICS