CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-025

MEDICAL REVIEW(S)

Medical Officer Review of IND Protocol
Division of Oncology Drug Products

IND #: 70774 serial # Pre-IND / Pre-NDA **PM**: DP
Letter Date: October 11, 2004 **30 day safety date:** NA

Application Type: Commercial
Drug(s): Topotect™ (Dexrazoxane HCl injection)
Drug Class: topoisomerase II inhibitor; chemoprotectant
Mechanism of Action: reduce normal tissue damage caused by doxorubicin, presumably by chelating iron and impairing free-radical generation by doxorubicin, leading to damage to myocardium
Drug Type: Approved agent for cardioprotection from doxorubicin
Related INDs: none
Protocol Number: none
Protocol Title: none
IND Sponsor: TopoTarget A/S, Denmark
Indication(s): anthracycline extravasation during chemotherapy
Principal Investigator:

Primary Reviewer: Robert C. Kane, MD (*Reviewer comments in italics.*)
Team Leader: Ann Farrell, MD

Background:
TopoTarget received Orphan drug designation in March, 2004, for Topotect, for treatment of anthracycline chemotherapy extravasation. Dexrazoxane is commercially available from Pfizer in the U.S. and Chiron in Europe (as well as a recent generic approval, Bedford Labs dexrazoxane). It has been used as an IV chemoprotectant administered just prior to doxorubicin IV. The sponsor has performed two clinical studies of the use of dexrazoxane as a chemoprotectant following extravasation of IV anthracycline and is planning to submit an NDA on the basis of the clinical results to date and supportive animal studies. The sponsor is not planning to manufacture the product.

The sponsor has already conducted one open-label single arm study and is completing a second, similar study at present.

> TT01 was open from 2001 to 2003 in 17 hematology-oncology centers in Denmark, in which 23 patients with suspected anthracycline extravasation were assessed and provided informed consent for the use of dexrazoxane, 1000 mg/m2 in D5/W over 1-2 hours, started within 6 hours of the event. Small tissue biopsies from the infiltration area were required at the start of treatment to look for tissue fluorescence, indicating the presence of anthracycline drug. Five patients did not receive additional doses because of negative tissue biopsies in 4 and no biopsy in one

patient with a central venous infusion device. Of the 23, 18 were treated within 6 hours of the event, and had a positive biopsy, and were evaluable for efficacy. A second dose of 1000 mg/m2 was given the next day to each of the 18, with a third dose on the third day at 500 mg/m2. Among these patients, 9 had received doxorubicin and 14 received epirubicin.

Of the 18 patients, none required surgical therapy, which the sponsor suggests is the standard of care in Denmark. The size of the infiltrated area was measured at the time of treatment; the mean area was 16 cm^2 with a range of 1 to 75 cm^2. No local or topical therapy was reportedly given. There is no other recognized therapy of benefit for this condition in Denmark or in the U.S.

TT02 is the second, international multicenter study currently open now to study at least 35 patients similar to TT01 above. The same entry requirements for suspected infiltration of an anthracycline within 6 hours, treatment over 3 days with the same schedule of dexrazoxane infusion, and monitoring are described. To date, 19 patients have been enrolled and 14 are evaluable for efficacy based on having positive skin biopsies for fluorescence.

Of the 14 evaluable, only one required surgery for treatment following the extravasation.

Assessment of adverse events is difficult because all of the patients are receiving chemotherapy concurrently and have AEs from the primary therapy.

Draft labeling has been provided by the company.

Issues:

Dexrazoxane is commercially available for the reduction of cardiotoxicity from doxorubicin only, and only in breast cancer patients after receiving 300 mg/m2 dose. Effectiveness has not been shown for this indication with other anthracyclines. The tissue protective effect is attributed to a reduction of free-radical species generated by the drugs of the anthracycline family which currently includes doxorubicin, daunorubicin, idarubicin, epirubicin, valrubicin, and mitoxantrone.

In this submission, the sponsor has chosen an arbitrary dose and schedule of dexrazoxane and reports reduction or elimination of the skin toxicity related to extravasation of doxorubicin and epirubicin when compared to historical controls. The sponsor also has asserted that a considerable number of such patients would have needed corrective plastic surgery to repair the damage which usually ensues following extravasation. A controlled study to confirm this benefit is not practical. The sponsor does not plan to study the drug in the U.S. Most

anthracyclines given in the U.S. today are given through an indwelling intravenous line such as a central venous access device in which extravasation is exceedingly rare except for certain occasions.

Consent Form: Not Included

Summary Statements – NOT APPLICABLE

a. The risks of the proposed study appear acceptable for patients with (type of disease)
b. The risks are adequately appreciated
c. Adequate precautions are being taken.
d. The consent form conveys the study rationale, potential risks, possible benefits and alternative treatments in a clear and logical manner. Assent for minors is not included.
e. The study objectives are reasonably clear and are based on a sound rationale.
f. The protocol may provide sufficient data to achieve the study objectives.

Recommended Regulatory Action – NOT APPLICABLE
This protocol is well-designed and may proceed
or
This protocol is well-designed and may proceed if the following deficiencies and comments are communicated to the sponsor and the sponsor agrees to correct the following deficiencies:
or
This protocol is well-designed and may proceed if the following deficiencies and comments are communicated to the sponsor and the sponsor agrees to correct the following deficiencies and submits an amended protocol:
or
This protocol is placed on clinical hold due to the following deficiencies:

Reviewer Background Notes:

Notes regarding the dexrazoxane dose:
In a phase 2 study of dexrazoxane for its anti-neoplastic potential in the treatment of AIDS-related Kaposi's sarcoma, 13 patients received 1000 milligrams/square meter/day for 3 days every 3 weeks, with dosage adjustment based on nadir granulocyte and platelet counts. One patient had an objective partial response after 7 courses of therapy, and 3 had subjective tumor regression. Duration of response was not reported. A significant incidence of neutropenia and thrombocytopenia necessitated dosage reduction in several patients (Chachoua A, Green M, Wernz J et al: Phase II trial of ICRF-187 in

patients with acquired immune deficiency related Kaposi's Sarcoma (AIDS-KS). Invest New Drugs 1989; 7:327-331.)

In a study in lung cancer, dexrazoxane was found to be ineffective as a single agent in the treatment of NON-SMALL-CELL LUNG CANCER. Intravenous doses of 1500 milligrams/square meter were administered for 3 consecutive days, repeated every 3 weeks, with dosage adjustment based on degree of myelosuppression. No antitumor activity was seen, despite the fact that the doses used were 20% higher than those used in previous studies (Natale RB, Wheeler RH, Liepman MK et al: Phase II Trial of ICRF-187 in non-small cell lung cancer. Cancer Treat Rep 1983; 67:311-313).

This information appears to support the safety of the sponsor's intended dose.

Dexrazoxane protection for epirubicin:
In a multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer, the incidence of cardiotoxicity was reduced from 23% to 7% with addition of dexrazoxane. No difference was found in RR, PFS or S. (Venturini M, Michelotti A, Del Mastro L et al: J Clin Oncol 1996; 14:3112-3120).

There is some clinical evidence for dexrazoxane cardiac protection for epirubicin.

At the sponsor meeting on November 9, 2004, the sponsor was advised that submission of the study findings will also require adequate evidence of outcomes to be expected in an untreated control group to support the treatment benefit. Also, the sponsor's nonclinical studies of cutaneous anthracycline protection would have to be reviewed in detail. Discussion of the fast-track and priority review procedures also was provided.

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/s/

Robert Kane
11/9/04 06:27:36 PM
MEDICAL OFFICER

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CLINICAL AND STATISTICAL REVIEW

Application Type	NDA 22-025
Submission Number	000
Submission Code	N
Letter Date	01/31/06
Stamp Date	02/01/06
PDUFA Goal Date	08/01/06
Medical Reviewer	Robert Kane, MD
Medical Team Leader	Ramzi Dagher, MD
Statistical Reviewer	Shenghui Tang, PhD
Statistical Team Leader	Rajeshwari Sridhara, PhD
Review Completion Date	July 17, 2006
Established Name	Dexrazoxane
(Proposed) Trade Name	Totect
Therapeutic Class	Chemo-protectant
Applicant	TopoTarget A/S
Priority Designation	P
Formulation	Intravenous
Dosing Regimen	1000 mg/m^2 daily times 2 days then 500 mg/m^2 on day 3
Indication	Anthracycline extravasation
Intended Population	Recipients of anthracyclines who experience extravasation

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Table 1: Abbreviations used in the review

AE	Adverse Event (CTC criteria)
CVAD	Central venous access device
CR	Complete response
CSR	Clinical study report
CTCAE	Common Toxicity Criteria, version 3, NCI
Dex	Dexrazoxane
Dox	Doxorubicin
ECOG	Eastern cooperative oncology group
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intention to treat population (all patients' randomized)
IV	Intravenous
LDH	Lactate dehydrogenase
NOS	Not otherwise specified
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	per os, orally
P.S.	Performance status
SAE	Serious adverse event (CTCAE criteria)
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant's proposed indication is: treatment of anthracycline extravasation during chemotherapy.

Because CMC and microbiology deficiencies remain involving site inspections, sterility and comparability protocols, I recommend that Totect be considered as "approvable" at this time.

Upon satisfactory resolution of these issues, I recommend regular approval for Totect for the indication: treatment of extravasation resulting from intravenous anthracycline administration.

This NDA for Totect is submitted as a 505b (2) application based on the reference drug Zinecard® (dexrazoxane for injection, Pfizer, Inc), which is FDA approved for reducing the incidence and severity of cardiotoxicity caused by doxorubicin therapy. The applicant, Topotarget A/S, has obtained a patent for a new method of use for the marketed drug, dexrazoxane, to treat anthracycline extravasation injury. Substantial evidence of effectiveness is provided by the very low incidence of required surgery (1 in 57 patients) and of other sequelae in the applicant's study population of patients with confirmed anthracycline extravasation who received Totect. While the true frequency of surgical intervention is uncertain in this population, this reviewer judges it is most likely that 10 – 25% of patients would have required surgery in the absence of Totect treatment to avoid necrosis or chronic morbidity. The applicant's two studies are single-arm in design and thus lack concurrent controls. However, historical evidence of the frequency of required surgery and data from the applicant's nonclinical studies support this approval recommendation.

The therapy appears safe for its intended use, although this conclusion also is based partially on external historical experience, since the two studies submitted for the NDA lack comparator arms. No irreversible morbidity or mortality resulted from Totect treatment in the two studies submitted. The benefits of this therapy appear to exceed the risks substantially.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

I recommend that the proposed proprietary name, Totect, be changed to avoid confusion with another drug, Topotecan. This suggestion was referred to DMETS in April 2006. As of July 16, 2006, this concern has not been resolved.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

In North America, anthracyclines usually are administered through indwelling central venous access devices (CVADs). This route was uncommonly used in the NDA study, and skin biopsies were not performed in this group to verify anthracycline extravasation. A post-marketing registry should be considered to monitor the results of the initial post-marketing experience in North American patients, including those who fulfill the criteria of suspected anthracycline extravasation while receiving their anthracycline through CVADs. This registry could provide additional supportive evidence for the efficacy of Totect as applicable to current clinical practice in North America. The registry should document the type of anthracycline, type and location of anthracycline infusion (site, central access line or peripheral line), estimated amount of anthracycline administered up to the time of event, time interval between the event and the infusion of the first Totect dose, the total dose of Totect given, and outcome of surgery required and sequelae of residual limitation of motion, pain, and necrosis.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Applicant's clinical studies for anthracycline extravasation

	N	Design	Population	Age (mean)	Gender M / F
TT01	23 entered / 18 evaluable	Open label, single arm	Cancer patients with suspected extravasation	57 years	5 / 13
TT02	57 entered / 36 evaluable	Open label, single arm	Cancer patients with suspected extravasation	55 years	12 / 24

The applicant has studied Totect in a single treatment course (of three days duration) in two similar, small, open-label, single-arm studies in patients suspected of experiencing anthracycline extravasation during IV chemotherapy infusions for malignancy. According to the applicant, anthracycline extravasation usually leads to tissue necrosis requiring surgical excision and grafting. The initial study, TT01, was planned to determine the rate of failure that would occur if Dexrazoxane were substituted for the usual surgical therapy employed routinely in Denmark following extravasation of an anthracycline. The extravasation event was confirmed by the applicant by performing tissue biopsies and showing fluorescence microscopically in the tissue under ultraviolet light. The applicant has previously determined fluorescence in tissue to be an indicator of the presence of anthracycline in tissue as described below. Based on a nonclinical model and previous literature describing human exposure to Dexrazoxane, the applicant chose 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 applicant enrolled 80 patients and considered 54 to be evaluable in the two studies. The principal reasons for patients being judged as not evaluable were failure to receive the first Totect dose within 6 hours of the event, failure to perform tissue biopsies, or the finding of no fluorescence in the tissue biopsy.

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, indicating that Totect therapy can spare most patients from the need for surgical intervention to treat anthracycline extravasation. These two studies comprise the NDA for Totect, along with nonclinical studies in rodents in support of the applicant's claims.

While the study findings are favorable, there are four uncertainties to be considered:

1. The studies conducted lack concurrent controls- direct efficacy and safety comparisons are not possible.
2. The results primarily describe a population of patients receiving anthracyclines through peripheral, small vein, temporary IV access around the wrist, hand, forearm and elbow. Most anthracycline administration in the U.S. now is performed via indwelling central venous access devices. Specially trained oncology nurses are alert for the possibility of extravasation and quickly stop infusions upon any signs of possible extravasation. Both factors have reduced the frequency and severity of extravasation injury and the need for subsequent surgical treatment.
3. The proportion of patients (with anthracycline extravasation) who require surgery remains uncertain both from the applicant's data as well as in contemporary U.S. practice.
    a. There are no standard guidelines or clear indicators guiding surgical intervention.
    b. The degree of tissue injury likely reflects the amount and concentration of anthracycline extravasated, but it is not possible in patients to quantitate the amount of anthracycline gaining access to peri-venous tissues.
    c. The applicant advises that, based on previous evidence, the usual standard of care in Denmark has been to test for extravasation and if fluorescence positive, all patients were operated on to resect the involved area.
4. The observed safety findings reflect primarily the patients' underlying disease processes (cancer) and the concurrent chemotherapy, not the therapy with Totect.

The applicant has provided the following replies to these concerns:

1. A controlled trial of this condition is not feasible or ethical
2. While there are no standard surgical intervention guidelines, and while surgical intervention was 100% in Denmark, surveys of other regions suggest surgical treatment rates may be in the range of 35% – 50% (applicant's estimate) although this is difficult to validate.

3. All evaluable patients (54) in the two studies had anthracycline present in tissue based on a positive fluorescence finding, confirming that extravasation had occurred.
4. Most patients' extravasations involved peripheral IV sites in the lower arms, wrists, and hands, which have been associated with the worst extravasation tissue injuries.

1.3.2 Efficacy

Totect appears to reduce substantially the risk of surgery and serous sequelae from anthracycline extravasation. In both studies, the primary endpoint was the reduction in need for surgical intervention to treat anthracycline extravasation-related tissue injury. Among a total of 80 patients enrolled in both studies, the applicant has concluded that only 1 of 54 evaluable patients required surgery after receiving Totect. I have determined that only 1 of 57 evaluable patients required surgical repair. Later sequelae of extravasation injury were mostly mild and did not adversely influence the benefit of Totect. Despite the lack of a control group, the extravasation conditions studied in TT01 and TT02, namely peripheral IV administration sites around the wrist, dorsum of the hand, and forearm, are notorious for serious extravasation tissue damage and frequent (although not universal) need for surgical resection and grafting. Surgical resection is the only recognized beneficial therapy for this event, but it remains uncertain which patients require surgery and when surgery should be performed. The frequency of required surgical intervention for extravasation is not well defined but is likely in the range of 10-25%. In some instances, a reluctance to commit to surgery may prolong or increase the degree of tissue damage. The applicant's results directly apply to doxorubicin and epirubicin but should be appropriate for all anthracyclines with vesicant properties. Although there were only 4 patients in the study with CVADs, the findings also are plausibly applicable to anthracycline extravasations involving central venous access devices.

The dose and schedule chosen are effective. The optimal dose and the duration of dexrazoxane therapy necessary to treat this indication are not clarified by the present studies using only one dose and schedule, and possibly a lower dose might be equally effective.

If an anthracycline extravasation appears likely, skin biopsies to examine for fluorescence should not be required before administering Totect. In the NDA, all patients had positive fluorescence on biopsy as a prerequisite to receiving the full Totect regimen. This assay is not routinely provided in clinical labs. If extravasation is uncertain, this option may be considered to verify the event. However, delayed administration of Totect beyond the 6 hour time limit may impair the benefit and should be avoided.

1.3.3 Safety

The study population available does not allow a direct quantitative assessment of the safety of dexrazoxane (Dex) for this indication since there is no concurrent control group and all patients are also receiving chemotherapy. The safety population is smaller than typically expected by

ICH guidelines.[a] Duration of exposure is not a relevant safety concern for this indication since patients receive only a single, three-day treatment. The two single-arm studies are comprised entirely of a population of adult patients with cancer receiving intravenous chemotherapy with an anthracycline and who are suspected of experiencing the event of anthracycline extravasation outside of the vein, and who then receive the study drug, Totect, Dexrazoxane (Dex). A single dosing regimen has been studied, consisting of Totect 1000 mg/m2/day for 2 days then 500 mg/m2 on the third day.

Reviewer calculation of Totect exposure by day of treatment

Day	Planned dose	Number of patients	Mean dose administered
0 (event day)	1000 mg/m2	80	996.7 mg/m2
1	1000 mg/m2	72	994.9 mg/m2
2	500 mg/m2	69	500 mg/m2

There is no control group available to isolate the possible adverse effects of the addition of Dex in this circumstance, and the morbidity of the underlying disease and chemotherapy toxicities confound the assessment of adverse events. No patients were reported to have experienced lethal or unexpected events after receiving Dex, and the adverse events observed are consistent with the typical findings in an adult population of cancer patients receiving multi-agent chemotherapy independent of receiving Totect.

Thus, for this indication, safety findings cannot be directly assessed, but may be indirectly estimated through literature reports of studies of single agent Dex administration conducted over 20 years ago. In some of those reports, Dex was given in a similar dose and schedule of daily times 3 days to assess its possible role as an antineoplastic agent. Temporary reductions in blood counts, temporary infusion site pain, nausea, and transient mild elevations in ALT and AST enzymes appear to be the predominant adverse effects related to single agent Dex infusion as discussed further below.

1.3.4 Dosing Regimen and Administration

The dosage form is powder in 500 mg vials and solvent for injection. [redacted] The route of administration is intravenous. The dose is 1000 mg/m^2 on day one, to be given as soon as possible and within 6 hours of the event, 1000 mg/m^2 on day 2, and 500 mg/m^2 on day 3. In the studies, the maximal daily dose was limited to 2000 mg (equivalent to a patient of 2.0 m^2 body surface area. The drug was infused over 1-2 hours in isotonic glucose solution, 1000 mL for day 1 and 2 then 500 mL on day 3. No other dosage schedules were studied.

b(4)

a ICH safety population recommendations include 1500 total with 300-600 for 6 months and 100 for one year.

1.3.5 Drug-Drug Interactions

None are known. Dex does not alter the PK of doxorubicin.

1.3.6 Special Populations

No patients under age 18 were studied. The mean age was 56 years (range 31 to 81 years) in the two studies. In total, 25% of the patients treated with Totect were age 65 years or older, and 14% were 75 and older. Race was not solicited but almost all patients were Caucasian as judged from the photographs of the injury sites and the geographic location of the studies.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Totect™ 500 mg powder and solvent for injection is TopoTarget's proprietary name for dexrazoxane for injection, previously known as ICRF-187. Dexrazoxane is currently marketed in the U.S. by Pfizer (formerly Pharmacia and Upjohn) under the brand name Zinecard® (the reference listed drug, NDA 20-212), and also as a generic product, Dexrazoxane for injection, Bedford Labs, approved under ANDA 76-068 in 2004. A patent infringement action by Pfizer against Bedford was dismissed after a settlement between the companies was reached in 2004. In Europe, a biopharmaceutically equivalent product, Cardioxane, manufactured by Chiron, Inc, is approved for use in the E.U.
Zinecard was FDA approved in 1995 under subpart H 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/m^2 and who will continue to receive doxorubicin therapy. It is not recommended for use with the initiation of doxorubicin therapy. Regular approval was granted in 2002 after further literature review. Typically, dexrazoxane (Dex) is given immediately before doxorubicin (dox) intravenously in a ratio (in milligrams) of 10:1 Dex:dox. In Europe, a 20:1 ratio is typical. Thus, in Europe, a typical schedule for cardioprotection in a patient receiving 50 mg/m2 of doxorubicin would include a single dose of 1000 mg/m2 of Dex given immediately prior to the doxorubicin. There is no reported overdose experience. This European dose ration was considered by the applicant in selecting the dose for the product.

The Zinecard label (2005) contains the following warnings:

- "Zinecard may add to the myelosuppression caused by chemotherapy
- There is some evidence that use of dexrazoxane concurrently with the initiation of doxorubicin therapy may interfere with antitumor efficacy (lower response rate and shorter time to progression) in a large breast cancer trial when used in this manner
- Second malignancies (AML) have been reported in patients treated chronically with oral razoxane, the racemic mixture of which dexrazoxane is the S(+) enantiomer"

Also in the label, "In a controlled study of patients receiving FAC chemotherapy, a comparison of the addition of dex versus placebo showed no notable differences in AEs except for more pain on injection reported on the dex arm for both cycles 1 and 7. Leukopenia, granulocytopenia and thrombocytopenia were more severe with the addition of dex, but recovery counts were similar for both groups. Some patients experienced marked abnormalities in hepatic or renal function tests, but the frequency and severity were similar for both groups."

The only contraindication noted in the Zinecard label is that Dex is contraindicated in patients who are not receiving an anthracycline.

2.2 Currently Available Treatment for Indications

There are no alternative medical treatments of recognized benefit for this indication. Anecdotal experiences with cooling, topical or injectable steroids, topical dimethyl sulfoxide (DMSO), and injections of bicarbonate or thiosulfate have been described without convincing evidence of benefit. In various percentages of patients, surgery has been used to resect the area of infiltration acutely or after some evolution of tissue damage. Dexrazoxane has not previously been reported to have been studied or approved for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Dexrazoxane for injection is commercially available in the U.S. and in Europe. The approved U.S. products are produced by Pfizer and Bedford labs. The applicant plans to obtain the finished product, dexrazoxane, [redacted] and does not plan to manufacture the drug product. b(4)

2.4 Important Issues with Pharmacologically Related Products

There are no related products.

2.5 Presubmission Regulatory Activity

A pre-IND meeting occurred on November 9, 2004. A pre-IND number 70774 was assigned but no IND was filed. This application is a 505b (2) submission and is referenced to NDA 20-212. Orphan drug designation was requested and granted by FDA "for dexrazoxane for the treatment of anthracycline extravasation during chemotherapy" on March 25, 2004 and 7 year market exclusivity has been requested.
In July 2005, a marketing application was submitted to EMEA and is under review.
A U.S. patent has been issued to the applicant claiming a method of use.

2.6 Other Relevant Background Information

Anthracycline extravasation (or infiltration) is a serious but unusual complication of intravenous chemotherapy. Extravasation is defined as an escape of drug from a blood vessel into the surrounding subcutaneous tissues. Certain drugs may produce tissue damage if inadvertently administered into tissues surrounding a vein due to leakage through the vein wall puncture site or following displacement of the tip of the IV administration needle through the vein wall during a chemotherapy infusion. This leakage allows direct contact of the chemotherapy agent with adjacent peri-venous tissues. Spread within these tissues is erratic and can include adjacent fascial planes, tendons, muscles, and nerves.

Usually, extravasation is identified by immediate swelling, pain, and redness at the site of infiltration, and the administration is immediately stopped. Subsequently, variable redness, further swelling, and blistering may occur, followed later by ulceration and tissue necrosis. Many local measures, such as ice packs, injection of steroids or bicarbonate solutions, topical steroids,

and DMSO have been tried to prevent tissue damage, but without clear evidence of success for any of these measures.

It can be difficult to verify if a drug extravasation has occurred. Symptoms may vary and may be delayed. The ensuing blistering, ulceration, pain, and necrosis may progress over a number of weeks. Surgical assessment and possible excision of the injured tissue are appropriate for progressive blistering, ulceration, induration, erythema, or persistent severe pain, but the decisions of when to intervene surgically and what margins of resection to use are empiric. Because of this adverse effect of some chemotherapy drugs, contemporary practice in the U.S. is to administer such chemotherapy agents through indwelling venous access devices such as ports or catheters placed to allow chemotherapy to infuse securely into central venous vessels (CVADs). Small veins in the area of the wrist, dorsum of the hand, antecubital space, or forearm, or in the area of tendons or joints, usually are avoided for infusion of such drugs due to the serious consequences which may occur if extravasation and subsequent tissue injury occur in these locations.

Drugs commonly associated with this tissue reaction are referred to as "vesicant" agents and include anthracyclines, vinca alkaloids, mitomycin C, mechlorethamine, and dactinomycin. Anthracyclines commercially available include doxorubicin, daunorubicin, epirubicin, and a related drug, mitoxantrone. In the U.S. today, anthracyclines are typically administered intravenously through a venous access device such as an implantable port, a subclavian catheter, peripherally inserted central catheter, or a tunneled venous catheter (Hickman type). Before these options were commonly available, anthracyclines had been given via a temporary IV needle puncture placed for the purpose of giving that day's treatment. After IV access, anthracycline chemotherapy is typically administered as a short IV infusion along with a fluid solution such as glucose or saline running in the same line providing rapid IV dispersal, dilution, and circulation of the anthracycline drug. These measures are typical to minimize the chance of an accidental extravasation of anthracycline agents.

The specific mechanism of anthracycline extravasation tissue injury is not understood. The lesion appears similar to a burn injury. The amount of tissue injury following extravasation can vary widely but likely reflects the concentration and the total amount of vesicant drug which has extravasated and contacted the peri-venous tissues. Some ensuing wounds require surgical debridement and tissue grafting, while some may be followed expectantly and may resolve with mild to moderate scarring and/or reduced flexibility. Literature references on anthracycline extravasation are 20-30 years old and antedate contemporary infusion practices.

The frequency of extravasation and the frequency of the subsequently required surgical intervention are uncertain in the U.S. for a number of reasons, including the fact that surgical decisions to intervene are not clarified and can vary regionally. A recent retrospective report from MD Anderson hospital in 2002 described an incidence of extravasation of 0.01% of chemotherapy infusions over a 6 year interval. Among 44 extravasation cases accrued over a 2 year interval, 15 were ascribed to paclitaxel and 12 to doxorubicin. Only 26/44 patients were referred to a surgeon. Of these 26, 10 patients had surgery performed for extravasation-related tissue injury. Of these 10 surgeries, the majority resulted from doxorubicin (personal

communication from the author). The authors stated that satisfactory wound healing without surgery occurred in all the others.[1]

A small study performed earlier in Denmark by investigators associated with the applicant provides some information to guide management of extravasation. Suspicion of extravasation was based on symptoms of swelling, redness, and/or pain at the administration site. Small tissue biopsies of the area were performed and tested for tissue fluorescence as described above. Positive fluorescence is interpreted as indicating the presence of anthracycline in the tissue outside the vein and thus confirming extravasation has occurred. According to the applicant, when extravasation is suspected, but the biopsy tissue does not show fluorescence, surgery appears not to be necessary. Among 22 patients suspected of having an anthracycline extravasation, 9 patients whose biopsy was negative for fluorescence were observed without intervention and none showed sequelae, while 13 patients with positive biopsies (i.e. fluorescence) had surgery intended to remove the damaged tissue area. Of these 13, despite surgery, 8 had sequelae such as skin ulceration, atrophy, or limitation of motion (Andersson AP and Dahlstrom KK, 1993).[2] Such surgery has often caused a delay in subsequent chemotherapy treatment cycles while awaiting adequate wound healing.

Table 2: Extravasation sequelae as related to tissue fluorescence

	n	Wound sequelae
Fluorescence negative (and observed)	9	0
Fluorescence positive and treated by resection	13	8
total	22	8

Reviewer's table, based on Andersson AP and Dahlstrom KK [1]

The applicant has advised FDA that the standard of care in Denmark for the past several years has been to perform tissue biopsies adjacent to suspected extravasation sites, to examine the biopsies for tissue fluorescence, and to proceed with surgery for those patients whose biopsies show fluorescence. Thus the percent of patients who might do well without surgery is not well defined.

Information on the safety of IV dexrazoxane (Dex) administered alone, as well as in combination with anthracyclines and other chemotherapies, is available in literature reports in which Dex was tested as a single agent anti-neoplastic. In a phase 2 study of dexrazoxane for its anti-neoplastic potential in the treatment of AIDS-related Kaposi's sarcoma, 13 patients received 1000 mg/m^2 per day for 3 days every 3 weeks, with dosage adjustment based on nadir granulocyte and platelet counts. One patient had an objective partial response after 7 courses of therapy, and 3 had subjective tumor regression. Treatment emergent neutropenia and thrombocytopenia necessitated dosage reduction in several patients.[3] In a study of single agent Dex in the treatment of non-small cell lung cancer, intravenous doses of 1500 mg/m^2 daily were administered for 3 consecutive days, repeated every 3 weeks, with dose adjustment based on degree of

myelosuppression. Neutropenia was dose-limiting.[4] In addition to marrow suppression, nausea, vomiting, diarrhea, stomatitis, and transiently altered liver function have been observed.

In the U.S., Dex has been approved to reduce doxorubicin cardiac toxicity at a milligram/m2 ratio of 10:1 (limited because of evidence of increased neutropenia at higher doses of Dex) given IV as a single dose prior to the anthracycline. In Europe, for cardioprotection, a 20:1 (Dex:dox) ratio is typical. There is no other information available on other possible protective effects of Dex for other organs or toxicities. Concern remains that the cardioprotection afforded by Dex may result from Dex reducing the availability of the anti-tumor activity of doxorubicin, which could also reduce the availability of that agent to the tumor and cause a tumor protective effect. This may have been the reason that one of the approval trials for dex showed a lower response rate and shorter time to progression of cancer in the group receiving concurrent Dex compared to control. Dex was not approved for use as initial therapy for cardioprotection, but only after patients reached 300 mg/m2 of doxorubicin in an effort to mitigate this concern regarding possible tumor protection.

At the time of Dex approval, the cardioprotective mechanism of action proposed for Dex was via an iron-chelating effect of the drug, thus reducing the availability of iron to participate in the generation of free oxygen radicals in turn leading to cardiac tissue damage. This action was separate from the presumed anti-neoplastic mechanism of action of anthracyclines in blocking topoisomerase II. More recent evidence indicates that Dex is also a topoisomerase II inhibitor. The molecular mechanisms of action with regard to cardioprotection and the tissue protective action in ameliorating extravasation injury are uncertain.

Another uncertainty is whether Dex conveys protective benefits for anthracyclines other than doxorubicin and for mitoxantrone. Dex is not approved for cardioprotection with any other anthracyclines, but there is some literature supporting that use with epirubicin. In a multicenter European randomized controlled clinical trial of 160 total patients to evaluate cardioprotection of dexrazoxane (10:1 ratio) versus no Dex in women receiving epirubicin chemotherapy for advanced breast cancer, the incidence of cardiotoxicity was reduced from 23% to 7% ($p=0.006$) with addition of dexrazoxane. Cardiac toxicity was defined as clinical signs of CHF, decrease in LVEF to $\leq 45\%$, or a decrease in resting LVEF of $\geq 20\%$ as measured by MUGA scans. Efficacy, assessed by RR, PFS, and OS was virtually identical with or without the addition of Dex.[5]

According to the applicant, it was not feasible to do parallel group placebo-controlled studies of extravasation, because:

(1) the event is infrequent and
(2) the accepted therapy in Denmark is early surgical intervention with resection of the affected area, based on earlier experience noted above.

Nonclinical studies in animals have been performed by the applicant and are included in the NDA to provide additional support for the applicant's hypothesis. No additional clinical testing has been conducted by the applicant beyond the two clinical studies included.

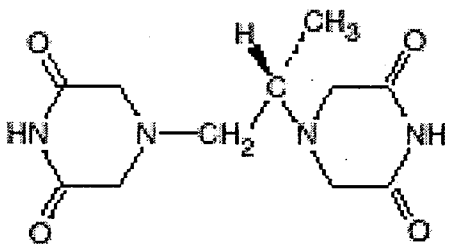
The applicant advises that, in Denmark, the standard of care following a suspected extravasation had been (1) to perform small biopsies in the periphery of the extravasation site, (2) to test these

samples for fluorescence microscopically, and then (3) to resect involved tissue as defined by the areas of positive fluorescence. The applicant also states that, since these two study results are so striking, the current standard of care in Denmark for suspected extravasation has changed now to the administration of dexrazoxane and no longer involves biopsies or surgery. If this product can safely and effectively eliminate or reduce the need for surgery or the development of wound complications following extravasation, this would constitute a clinical benefit.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The drug structure is shown here. Dex is the water soluble S-(+) enantiomer of racemic razoxane (ICRF-159) designed as a cyclic analog of EDTA. Dex is reported to cross cell membranes rapidly and then is converted to an open ring active form intracellularly.



CMC and microbiology deficiencies have been identified and communicated to the applicant by Drs. Leon Epps and Anastasia Lolas, the primary reviewers. The remaining issues include:

1. The primary packaging/labeling site is not ready for inspection
2. Three foreign sites have not yet been inspected
3. Unresolved issues remain with the comparability protocol for the addition of an alternative manufacturing site
4. An unresolved issue with the reconstitution procedure
5. AE recommendation from Team Microbiology from microbial product quality perspective

Please see the discipline reviews for further details.

3.2 Animal Pharmacology/Toxicology

Please see the review by Dr. David McGuinn. Several nonclinical studies in rodents have been conducted by the applicant to provide evidence of Dex protection from anthracycline tissue injury.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The NDA clinical data consists of 17 paper volumes, including paper CRFs and narratives, two PowerPoint slide sets of the extravasation sites of patients in the TT01 and TT02 studies, draft labeling in electronic format, and an excel spreadsheet of clinical data. Two single-arm, open-label European studies, TT01 and TT02 comprise the clinical data.

TT01 was conducted entirely In Denmark. TT02 was conducted in Denmark, Germany, Italy, and The Netherlands.

4.2 Tables of Clinical Studies

Table 3: Reviewer table of applicant's studies in the NDA

	N	Design	Population
TT01	23 entered / 18 evaluable	Open label, single arm	Cancer patients with suspected extravasation
TT02	57 entered / 36 evaluable	Open label, single arm	Cancer patients with suspected extravasation

In the two studies, a total of 80 patients were enrolled and 54 were judged evaluable by the applicant.

4.3 Review Strategy

The data consists of two small series of cases enrolled on study on the basis of a clinical suspicion of an anthracycline extravasation. No control group or contemporary experience outside of the two studies is provided except to note that the applicant asserts that the standard of care in Denmark at the time of the studies has been to treat all such extravasations surgically by resecting tissue affected by anthracycline extravasations. Thus this review consists of an evaluation of the descriptions of the patients and review of the photographic data, assessments of the likelihood that they did sustain the event (extravasation), subsequent non-surgical course, dosing, and assessment of safety in this context based on the reported information. In addition, a literature review was performed seeking data on the frequency of anthracycline extravasation and management strategies. Literature also provided information on the AE profile of single agent Dex.

In addition, I contacted two cancer centers, the MD Anderson cancer center and the Moffitt cancer center, regarding recent experience with chemotherapy extravasation. I also contacted the manufacturers of Doxil® and Ellence® (epirubicin) for any information they could provide on the frequency and management of extravasation injury for their products.

4.4 Data Quality and Integrity

A debarment certification is included.
DSI audit has been performed for the two principal study sites in Denmark. No material deficiencies in data or study conduct have been found.
The applicant has attested to no financial conflicts of interest with the investigators.

Although not pre-planned, the applicant requested and received an independent committee audit of the two studies by [redacted] b(4)

[redacted] The committee was presented with complete extracts from the clinical databases, the completed CRFs, and the photo documentation. The committee did not see the hospital charts themselves.

4.5 Compliance with Good Clinical Practices

The applicant reports that for both studies, protocols and written consent forms were submitted and approved by independent ethics committees and the studies were conducted in accord with ICH/GCP and the Helsinki declaration.

4.6 Financial Disclosures

The sponsor certifies that it did not enter into any financial arrangements with the investigators and has included form FDA3454. No financial interest forms have been submitted by the individual investigators.

5 CLINICAL PHARMACOLOGY

No studies were conducted by the applicant for this NDA submitted under section 505b(2). Please see the primary OCPB review by Dr. Gene Williams. Information from the Zinecard label was adapted for this section.

APPEARS THIS WAY ON ORIGINAL

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant's proposed indication is: "treatment of anthracycline extravasation during chemotherapy."

The specific elements of the indication which I have considered are:
(1) The extravasation event including site, likelihood of the event actually having occurred, magnitude of the extravasation event, and timing of therapy following the event
(2) Evidence demonstrating the ability of Totect to limit or prevent tissue necrosis or other damage requiring surgical intervention,
(3) Applicability of Totect for anthracyclines as a drug class or for specific agents and
(4) Relevance of this experience to contemporary U.S. practice
(5) Could Dex possibly protect or reduce the tissue damage of any other vesicant extravasations if the mechanism of action is not specifically related to an anti-anthracycline effect

6.1.1 Methods

Literature review, examination of all photo sets provided, compilation of the descriptive findings in the excel database, and examination of the clinical study reports. In addition, the applicant presented the study findings to the Division with opportunity for questioning. To assess the safety of Dex, I examined literature reports of single-agent Dex studies from the 1980s. External consultation with Dr. Steven Libutti, a surgeon at the NIH, was obtained also.

6.1.2 General Discussion of Endpoints

The applicant's primary endpoint is the same in both studies:
"The prevention of need for surgical intervention following suspected anthracycline extravasation and its sequelae"

Surgical intervention was to be based on judgment of a plastic surgeon based on the development of tissue blistering and necrosis at the event site.

Secondary objectives are to:

- Avoid postponement of subsequent chemotherapy treatment cycles
- Evaluate and describe subsequent symptoms in the damaged area following Totect therapy for the event
- Evaluate tolerance/toxicity of Totect used in this schedule

Secondary endpoints also included assessments later in time for sequelae of tissue injury such as sensory disturbance, pain, skin atrophy, and limitation of movement.

In addition to considerations of the specific endpoints selected, the endpoints have to be judged in the context of the study designs. There are limitations to the conclusions that can be drawn

from this study design, namely single-arm, open-label, small studies, performed primarily in one practice area. Without a simultaneous control group, efficacy conclusions depend on the likelihood that the patients studied would have had serious wound complications and required surgery if they had not received Totect. Likewise, in the absence of a control group, safety of the product can only be inferred from prior single agent literature experience.

6.1.3 Study Design

The design of the two studies is similar. Each consists of a single arm, open-label, non-randomized study of sequential eligible patients. Dexrazoxane was provided by the two manufacturers: Chiron supplied Cardioxane® for TT01, and Pfizer provided Zinecard® for TT02. (Literature indicates that the two products are bioequivalent.)

Major eligibility elements for both studies were:

- receiving anthracycline anti-cancer therapies who
- exhibited a suspected anthracycline extravasation
- extravasation was suspected based on at least one of the following: immediate symptoms of pain, swelling, and/or redness related to receiving an anthracycline drug via a peripheral IV or central venous access device
- skin biopsies were performed to determine anthracycline-fluorescence in tissue
- anthracycline fluorescence was detected in tissue
- Totect therapy began within 6 hours of the event

Exclusion criteria were:

- known allergy to Dex
- age < 18 years
- performance status > 2 (ECOG)
- contemporaneous extravasation of other chemotherapy drugs such as vincas or mitomycin C
- Liver functions > 3 times normal (within 5 days or before 2nd dose of Dex)
- Neutropenia or thrombocytopenia > grade 2 CTCAE
- pregnant or nursing women or women of childbearing age not agreeing to contraception
- Use of topical DMSO in TT02 only

TT01 was conducted in 16 Danish hospital oncology departments.
All eligible patients had to have skin biopsies and confirmation of the presence of anthracycline in tissue (defined as positive tissue fluorescence). If biopsy fluorescence was not present (negative), patients were not given additional Dex and were not assessed for efficacy but were assessed for safety analysis. After informed consent, patients began Totect (as soon as possible and within 6 hours of the event). Totect was given by IV infusion over 1-2 hours for 3 consecutive days, 1000 mg/m2 on the day of the event, 1000 mg/m2 24 hours later, and 500 mg/m2 on the third day. Patients were followed for up to 90 days. Those showing signs of worsening skin reaction, defined as blistering or necrosis, were to have resection performed for blistering or necrosis according to the surgeon's judgment. Color photographs were performed serially on each patient. In the statistical plan, the applicant would declare Totect effective if operation could be avoided in 20 of 25 patients (80% avoidance of surgery rate) in contrast to the

standard Danish practice in which 100% of patients with fluorescence would have had surgical therapy based on the Danish standard of practice.

TT02, also a single-arm open-label study, was conducted subsequent to TT01 using a similar protocol and assessment plan, in Denmark and in additional countries. The applicant's statistical assumption was that approximately 35%-50% of patients in neighboring countries were receiving surgical management of anthracycline extravasations, and success would be defined by a reduction of the rate of surgery to less than 10%. The calculated sample size was 32 and the intention was to enroll 35 eligible patients.

For each study, the sponsor solicited an independent review of the patient data and conclusions by a committee of the Rigshospitalet, Copenhagen. (The committee concurred with the sponsor's findings and conclusions for each study.)

6.1.4 Efficacy Findings

In the two studies combined, a total of 80 patients were enrolled and 54 were judged evaluable by the applicant.

	N	Design
TT01	23 entered / 18 evaluable	Open label, single arm
TT02	57 entered / 36 evaluable	Open label, single arm

Table 4: Reviewer summary of applicant's efficacy findings in the two studies

	N	Design	n - requiring surgery	n - with sequelae
TT01	23 entered (14 epirubicin / 9 doxorubicin)	Open label, single arm		
	4 – biopsy negative			
	1 – no biopsy (CVAD)		0	0
	18 evaluable		0	2
TT02	57 entered (31 epirubicin / 24 doxorubicin / 2 Daunorubicin [1])	Open label, single arm		
	9 – biopsy negative			
	4 – no biopsy (3 with CVADs)			
	8 – protocol violations (see below)			
	36 evaluable		1	13

1: 2 patients received daunorubicin, one in a liposomal pegylated form
CVAD- central venous access device
See tables 9-10 for more details regarding the sequelae

Table 5: Reviewer summary of demographic and outcome findings in the applicant's 54 evaluable patients

Study	TT01	TT02
Number enrolled N	**23**	**57**
number evaluable (applicant) n	**18**	**36**
Gender: male / female	5 / 13	12 / 24
Age: mean (range in years)	57 (41-76)	55 (34-81)
Anthracycline:		
Epirubicin	11 (61%)	20 (56%)
Doxorubicin	7 (39%)	16 (44%)
Baseline symptoms:		
Swelling	16 (89%)	29 (81%)
Redness	14 (78%)	28 (78%)
Pain	7 (39%)	16 (44%)
Blisters	2 (11%)	0
Baseline area of lesion cm^2 median (range)	24 (1.0-75)	25 (1.0-253)
Outcomes		
Surgery required	0	1 *
Necrosis (and later surgery)	0	1 **
Sequelae judged greater than 'mild'	0	1

* Surgery performed on day 13
** This patient was excluded for protocol violations from the 36 evaluable but is noted here
** This patient also required surgery

Reviewer comment: Among all 54 patients judged evaluable by the applicant for the primary endpoint, one patient (1/54, 2%) required surgical intervention. One additional patient of the 80 enrolled, who was judged as not evaluable because of protocol violations, also required surgery.

Table 6: Anthracycline agents used and other chemotherapeutic drugs administered in the same IV access before anthracycline, TT01 and TT02

	TT01 (N = 23)	TT02 (N = 57)
Anthracycline		
Doxorubicin	9 (39.1%)	24 (42.1%)
Epirubicin	14 (60.9%)	31 (54.4%)
Daunorubicin	0	1 (1.8%)
Pegylated liposomal daunorubicin	0	1 (1.8%)
Any other chemotherapy agent	13 (56.5%)	31 (54.4%)
Cyclophosphamide	5 (21.7%)	18 (31.6%)
Vincristine/Vinblastine	7 (30.4%)	18 (31.6%)
Fluorouracil	3 (13.0%)	7 (12.3%)
Mabthera	0	4 (7.0%)
Prednisolone	0	2 (3.5%)
Bleomycin	1 (4.3%)	1 (1.8%)
Cisplatin	0	1 (1.8%)
Cytarabine	0	1 (1.8%)
Ifosfamide	0	1 (1.8%)

Sponsor table 2.7.4-4, module 2

Reviewer note: Patients receiving other vesicant chemotherapy via the same IV line were considered not evaluable by the applicant.

In TT01, 23 patients were enrolled, 18 females and 5 males, median age of 53 years. One patient, with extravasation from a central venous catheter, did not have biopsies performed and was judged not evaluable for efficacy by the applicant. In this patient, the evidence for extravasation was the appearance of red liquid from the catheter's skin penetration site after administration of anthracycline but without pain or redness of skin. Fluid aspirated from this cutaneous extravasation site was determined to be positive for fluorescence. (See table below.) Four patients of the 23 had biopsies performed in which the fluorescence test was negative. These four did receive one dose of Totect while the biopsy was being processed. The applicant also elected to exclude these four patients from the efficacy analysis, leaving 18 patients (78%) evaluable for the efficacy endpoint. Of the initial 23 patients, the anthracycline was epirubicin in 14 patients (60%) and doxorubicin in 9 patients (40%). This is consistent with European anthracycline usage. Seven patients (30%) had received a vinca drug just prior to but separate from the anthracycline infusion, potentially adding to the possibility of tissue injury from more than one drug. The estimated amount of anthracycline infused varied. Of the 18, 15 reported immediate extravasation symptoms of swelling and 15 reported redness. Severity of the extravasation was judged separately by the patient and by the investigator.

No patients had surgical resections, and all were judged to have satisfactory healing and recovery from the extravasation event. Two patients died from progressive cancer after 28 days but before the 90 day follow-up. The company advises also that an independent review committee met in 2003 and concluded that, in TT01, no patients were operated on and no patients had severe sequelae as of day 90. (All case report forms are included in appendix 16.3.1, module 5.) The

sponsor performed an interim statistical analysis after the 17th patient was evaluated. The sponsor concluded that 0/17 failures indicated that the likelihood that surgery was required with Totect therapy was less than 0.05. None required surgery, and the one patient with some wound necrosis, which healed spontaneously, was determined to have the necrosis in the area of and as a result of the biopsy procedure and not the extravasation.

Table 7: Reviewer table - Demographics of 18 patients biopsy-positive for fluorescence assessed in TT01

	Age	Cancer Dx	Anthracycline/ approx. amount infused [1]	Other drugs[2]	Symptoms[3]	Size of extrav-asation[4]	Time to Totect[5] (hrs:min)
010101	60	Breast	epirubicin 90%	no	S, R	1.0 X 1.5	5:50
010102	47	Breast	epirubicin 25%	no	S, R	4.0 X 2.5	5:55
010103	56	Breast	epirubicin 100%	No	S, R	8.0 X 5.0	4:20
010104	68	gastric	epirubicin 100%	5-FU	- R, P	5.0 X 1.0	4:00
010201	55	Lymphoma	Dox 50%	Vcr	S, R	8.0 X 4.0	4:45
010202	45	Lymphoma	dox 100%	B, Vlb	- R	9.0 X 6.0	5:40
010301	41	Breast	Epirubicin 100%	5-FU	S, R	4.0 X 4.0	4:45
010401	76	Lymphoma	Dox 30%	Vcr	S, R, - Bl	5.0 X 3.2	2:40
010402	47	Lymphoma	Dox 100%	C, Vcr	S, R	5.0 X 10.0	3:40
010403	73	Lymphoma	Dox 20%	Vcr	S, R	7.5 X 10.0	3:50
010601	53	Lymphoma	Dox 20%	No	S, R	3.4 X 3.8	2:00
010602	71	Breast	Epirubicin 10%	No	- R	4.0 X 7.0	1:55
010701	54	Breast	Epirubicin 100%	No	S, - - Bl	2.0 X 5.0	4:15
010702	53	Breast	Epirubicin 17%	No	S - -	6.2 X 5.8	4:15
010801	53	Lymphoma	Dox 90%	No	S, R	4.0 X 4.0	5:25
011301	62	Breast	Epirubicin 100%	no	S, R	2.0 X 2.2	3:25
011601	62	Breast	Epirubicin 90%	No	S, - P	1.0 X 1.0	2:40
011702	42	Breast	Epirubicin 100%	C,5FU	S, R	5.0 X 3.0	2:10
010203*	77	Myeloma	Dox 99%	Vcr	- -		5:50

1. Estimated amount of anthracycline infused at the time of the extravasation; Dox, doxorubicin
2. 5-FU, fluorouracil; Vcr, vincristine; B, bleomycin; Vlb, vinblastine; C, cyclophosphamide
3. S, swelling; R, redness; P, pain; Bl, blistering
4. in centimeters
5. Time from extravasation to beginning of Totect infusion

* This patient (# 19) was not biopsy-positive. Patient had a central venous catheter with reddish-color fluorescence-positive fluid observed leaking from the skin penetration site of the Hickman-type CVAD. See table 11 also.

Reviewer comments: I have included the one patient with the CVAD (#010203) in the efficacy population for a total of 19 evaluable cases. None of the above 19 patients were treated by surgical resection. None were considered to have experienced serious sequela of the extravasation. None discontinued Totect treatment. One patient was reported to have developed a staphylococcal wound infection with a 2.0 X 3.0 area of necrosis in a biopsy site on day 16 post extravasation and required antibiotic therapy. While there was subsequent complete wound

healing, this patient was scored as an incomplete response on the basis of continuing pain and dysesthesia of grade 1 at 90 days follow-up. The applicant reasonably concluded that the sequelae were related to the infection of the biopsy site and not the extravasation event. All other patients were considered as complete responders to Totect, with no serious sequelae (see table 9). Two patients had mild sequelae, including the one patient with the biopsy-related necrosis. Of the 18 patients, 12 continued their planned chemotherapy without a delay incurred by the extravasation. Of the 6 whose next treatment cycle was delayed, the mean delay duration was 8.7 days. Of the 18 patients, 16 were able to be followed for at least 90 days to confirm continuing success.

In TT02, 57 patients were entered and 36 were considered evaluable for efficacy by the applicant (see table 7). In TT02, 75% of the patients were enrolled from Denmark. One patient was entered twice because of two separate extravasation episodes. In nine patients, the biopsies were subsequently determined to be negative for fluorescence. Four patients had no biopsies performed (3 of whom had CVADs). One patient received only 2 days of therapy and withdrew for personal reasons. (This patient indicated only that she was not returning for the day 3 infusion without providing further explanation. She was telephoned subsequently and reported no necrosis or complications had occurred.) Two patients received therapy starting more than 6 hours post event (one at 2 days and one at 3 days). Two patients received other treatment considered by the applicant to interfere with assessing Totect effect. One patient lacked adequate description of the event as well as photographic documentation. One patient did not receive day 3 because of adverse events on day 1 and 2 (dizziness and somnolence). One additional patient received a total of 5 days of Totect, the last 3 at the 500 mg/m2 daily dose, on the basis of concern that the initial Totect schedule may have been suboptimal because of concurrent cooling of the site. Of note, this patient subsequently required surgery for necrosis on day 43 and then again subsequently. Ten patients had a delay in the subsequent chemotherapy cycle. For these 10, the delay was a mean of 10 days (range 7 to 15 days). Of the applicant's 36 evaluable patients, 34 were able to be assessed for at least 75 days after the event.

The anthracycline chemotherapy and other concomitant chemotherapy given just prior to the anthracycline are tabulated in table 8 for both studies.

Study TT02 enrolled 57 patient events, but only 36 patients were judged evaluable by the applicant, as shown below.

Table 8: Reviewer table – Applicant's disposition of patients in TT02 (57 events in 56 patients)

57 enrolled	
1	One patient with 2 events
- 9	Fluorescence negative
- 4	No biopsies performed
- 7	Protocol deviations-violations
36	Evaluable patients

From data in section 5.3.5.2.2

The 21 patients in table 8 judged non-evaluable by the applicant in TT02 are listed here

Pt No	Reason for exclusion
020101	biopsies for fluorescence negative
020304	biopsies "
023303	biopsies "
024002	biopsies "
024004	biopsies "
024501	biopsies "
024805	biopsies "
025303	biopsies "
024203	Only one biopsy weakly positive; classed as fluorescence negative biopsies [A]
020302	Protocol deviation: No biopsies performed
023101	Protocol deviation: No biopsies performed
023302	Protocol deviation: No biopsies performed
025002	Protocol deviation: No biopsies performed [A]
020801	Protocol deviation: Other treatment interfering with protocol administered [B]
025402	Protocol deviation: Other treatment interfering with protocol administered [B]
024301	Protocol deviation: Started treatment 5 days after extravasation
024304	Protocol deviation: Started treatment 3 days after extravasation
024305	Protocol deviation: Positive biopsies, but re-treated as 024306 only one week after first extravasation
024306	Protocol deviation: Positive biopsies, but received prior treatments as 024305 only one week before second extravasation
024204	Protocol deviation: initial photo documentation and description of event insufficient
024003	Protocol deviation: Only received 2 days of treatment, due to patient declining day 3

A: CVAD device used
B: Topical DMSO was used, a protocol exclusion in TT02

One patient (023201) in TT02 was determined to require surgery for necrosis and eventually had severe sequelae of pain, dysesthesia, and limitation of motion. This patient received Totect per protocol with the first dose approximately 4 hours after the event. The only factors possibly accounting for the failure are the combination of a large area of extravasation (252 cm2), site in the dorsum of the left hand and peripheral vein access. Swelling and redness was evident immediately after completion of infusion of 85 mg of epirubicin. Of the 57 enrolled, 54% received epirubicin and 42% received doxorubicin. One patient received daunorubicin, and one received a pegylated liposomal daunorubicin; however, neither was judged as evaluable by the applicant due to factors noted above. Also, similar to TT01, 32% (18 patients) had received a vinca drug prior to start of the anthracycline infusion. Of the 57 enrolled patients, 27 (47%) had breast cancer and 16 (28%) had lymphoma.

Sequelae, as assessed by the investigators during followup visits, were reported by the applicant to be present in 13 (36%) patients in TT02 at the last follow-up, which occurred 74-133 days following the start of Totect. However, these observations were not pre-specified as to type or grading system to be used to describe the sequelae. A secondary efficacy endpoint was the ability of Totect to prevent late sequelae as assessed serially in the interval from 1 to 3 months after the event. Sequelae reported in TT01 and in TT02 (possibly indicating reduced efficacy) are tabulated below. Sequelae assessments were performed by the individual investigators.

Hospitalization and delay in subsequent chemotherapy were also considered as sequelae by the applicant. The applicant was queried regarding possible "flare" reactions or aggravation of the injury site when further chemotherapy was resumed. Although this was not formally studied, no evidence for either effect was observed.

Table 9: Reviewer table - Clinical sequelae reported in TT01 and TT02 in 54 evaluable patients

Event	TT01 n=18	TT02 n=36
	n (%)	n (%)
Patients with at least one	2 (11%)	13 (36%)
Pain	1	9 (25%)
Sensory disturbance	2	7 (19%)
Skin atrophy	1	4 (11%)
Limited movement	0	3 (8%)
disfigurement	n/a	1 (3%)

See module 2.7.3 page 4 n/a = not assessed

Reviewer comment: Specific guidance on the assessment of sequelae was not provided in the protocol. All were graded as mild except for one patient with multiple sequelae. The next table describes similar findings in the non-evaluable patients and indicates no selective censoring.

Table 10: Reviewer table - Necrosis and clinical sequelae in the non-evaluable patients

Event	TT01	TT02
N = total / evaluable	23 / 18	57 / 36
Number of patients not evaluable (NE)	5	21
NE number with: at least one sequela	0	5/21
necrosis	0	1/21
pain	0	2/21
Sensory disturbance	0	1/21
Skin atrophy	0	1/21
Disfigurement	Not assessed	1/21

Table 11: Reviewer table - Sites of extravasation for all 80 patients

Location of extravasation	TT01 and TT02 N (%)
Forearm	50 (63%)
Hand	17 (21%)
Antecubital	9 (11%)
CVAD *	4 (5%)
Total	80 (100%)

* CVAD, central venous access device, see table 12 also

Among all 80 patients in both studies, the locations of the extravasations involved the hand in 17 patients, the forearm in 50, the antecubital fossa in 9, and a central venous access device in 4 patients. Most events occurred in early treatment cycles, including 25% in cycle 1 and 59% in total by cycle 3. Swelling and redness were usual; pain and blistering were unusual indications of extravasation. The majority of patients were female (74%) and the mean age was 55 (range 21 – 92 years).

Table 12: Reviewer table - Characteristics of the four patients with CVADs *

PTID	device	Biopsy?	Drug	symptoms	Surgery
01-0203	Hickman-type	No – fluid positive	Doxorubicin 50 mg	Red liquid emerged from the skin site after 100% of dose	No
02-4203	Hickman-type	Yes – one weakly positive	Doxorubicin 54 mg	Swelling only after infusion of 100% dose	No
02-5002**	Implanted port	Yes-positive	Liposomal doxorubicin 84 mg	Swelling and redness with the infusion of 50% of intended dose	No
02-5402	Tunneled catheter	Yes – positive	Doxorubicin 18 mg and vincristine planned as a continuous infusion	Redness 36 cm^2 area after receiving 10% of intended dose	No

* CVAD, central venous access device
** Patient was judged evaluable by the applicant and counted in the TT02 efficacy group

Reviewer comment: A total of 4 patients in the two studies had CVADs. Patient 02-5002 was included in the efficacy population. According to the applicant, patient 01-0203 was excluded because of no biopsy performed, patient 02-4203 was excluded because of one of only two biopsies reported as weakly positive, and patient 02-5402 was excluded because of receiving 2 drugs simultaneously in the IV infusion. This reviewer considers all 4 patients evaluable for efficacy. This increases the efficacy population to 57 in total. None of these 4 patients required surgery.

Reviewer comments: The applicant reported that only 1 patient of the 54 considered evaluable (0/18 from TT01 and 1/36 from TT02) required surgery for necrosis after receiving Totect. This reviewer concludes that zero of 19 patients in TT01 and one of 36 in TT02 received surgery for necrosis after Totect therapy (1/55). One additional patient in TT02, excluded on the basis of a protocol specified violation because of receiving concomitant local cooling along with Totect, and who also received 5 days of Totect because of concern about the cooling procedure causing impairment of Totect efficacy, later also required surgery for necrosis.

Equally important, none of the 4 patients in TT01 who were assessed as fluorescence-negative, and who received only one dose of Totect in TT01, later developed necrosis over a minimum 3-4 week followup. Also, none of 9 patients who were fluorescence-negative in TT02 developed necrosis. However, of these 9 in TT02, 4 patients received one day of Totect while 5 patients received all 3 days due to time delays in assessing the biopsies for fluorescence. Thus, none of 13 patients suspected of having an extravasation but found to be fluorescence-negative developed necrosis, although all received at least one day of Totect therapy.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions by reviewer

Reviewer Efficacy results

	N	n - requiring surgery	n - with sequelae [2]
TT01	23 entered		
	4 – biopsy negative		
	1 – no biopsy (CVAD) 1 added back in	0	0
	19 evaluable	0	2
TT02	57 entered		
	9 – biopsy negative		
	4 – no biopsy (2 with CVADs) 2 CVAD patients added back in		
	8 – protocol violations (see below)		
	38 evaluable	1	13

Reviewer total = 57 eligible
one failure requiring surgery (1/57)

56

In TT01, I added one patient (010203) back into the evaluable population for a total of 19 evaluable. In TT02, I added back 2 patients (024203 and 025002) to the evaluable population for a total of 38. Combining both studies, the total evaluable group was 57 patients, in which one required surgery.
Totect appears to reduce substantially the risk of surgery and serous sequelae from anthracycline extravasation. Most patients described swelling and/or redness indicating the event. Almost all

patients received the intended treatment schedule. According to the applicant, 1 of 54 evaluable patients (2%) required surgical intervention. According to this reviewer's analysis, only 1 of 57 (2%) patients required surgery for complications of anthracycline extravasation. Despite the lack of a control group, the circumstances studied in TT01 and TT02, namely peripheral IV administration sites around the wrist, dorsum of the hand, and forearm, are notorious for serious extravasation tissue damage and frequent (although not universal) need for surgical resection and grafting. Surgical resection is the only acknowledged therapy for this event, but it remains uncertain which patients require surgery and in some instances, a reluctance to commit to surgery may prolong or increase the degree of tissue damage. The applicant's results directly apply to doxorubicin and epirubicin but should be applicable for all anthracyclines with vesicant properties. Although there were only 4 patients in the study with CVADs, the findings also are plausibly applicable to anthracycline extravasations involving various central venous access devices.

During the conduct of both studies in Denmark, the applicant was able to identify only 2 additional patients who had suspected anthracycline extravasations but were not enrolled. One was judged not eligible because of psychiatric reasons and the other patient had already received Totect. Thus there is no evidence that the applicant selected patients for the study who might not be representative of typical conditions in Denmark (n.b., 75% of all patients in both studies came from Denmark). In addition, the sequelae experienced by patients considered non-evaluable by the applicant did not differ in frequency or severity from those who were evaluable.

The dose and schedule chosen are effective. The optimal dose and duration of dexrazoxane therapy for this indication are not clarified by the present studies using only one dose and schedule.

If an anthracycline extravasation appears likely, skin biopsies to examine for fluorescence should not be required before administering Totect. In the NDA, all patients had positive fluorescence on biopsy as a prerequisite to receiving the full Totect regimen. This assay is not routinely provided in U.S. clinical labs. If extravasation is uncertain, this option may be considered to verify the event. However, delay beyond the 6 hour time limit for administration of Dex may impair the benefit and should be avoided.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in TT01. There were 3 deaths in TT02, occurring at 2, 2.5, and 4 months after Totect therapy. None were considered Totect-related by the applicant or this reviewer.

7.1.2 Other Serious Adverse Events (SAEs)

In TT01, 12 SAEs were reported for 7 different patients. Only 4 were plausibly associated with Totect. One febrile neutropenia, one pancytopenia, one pain with edema at the Totect infusion site, and one extravasation of Totect were reported.

Hospitalization was not counted by this reviewer since several patients were hospitalized for their convenience and for study purposes and not for medical necessity. See table below.

Table 13: Summary of SAEs in TT01

Patient no.	Event	SOC/Preferred Term (MedDRA)	Outcome	Relationship
010104	Broken leg	Injury, poisoning & procedural complications/fracture	Resolved with sequelae	Not related
010105	Pancytopenia	Blood and lymphatic system disorders/pancytopenia	Resolved	Suspected
010203	Fever and nausea	General disorders and administration site conditions/ pyrexia Gastrointestinal disorders/nausea	Resolved	Unlikely
	Vomiting and nausea	Gastrointestinal disorders/vomiting/nausea	Resolved	Not related
010402	Infection, Febrile neutropenia. Neutropenia	Blood and lymphatic system disorders/neutropenia Infections and infestations/ postoperative infection General disorders and administration site conditions/ pyrexia	Resolved	Possibly related
	Pneumonia	Infections and infestations/pneumonia	Resolved	Not related
010602	Tumor progression	Not coded	Resolved	Unlikely
	Tumor progression	Not coded	Resolved	Unlikely
	Tumor progression	Not coded	Resolved but patient remains hospitalized	Not related
010801	Edema and pain in TT arm	General disorders and administration site conditions/injection site phlebitis	Resolved	Definitely related
011702	Extravasation of dexrazoxane	Not coded	Resolved	Definitely related
	Infection around biopsy	Infections and infestations/wound infection staphylococcal	Ongoing wound is 7 x 7 mm at day 90. At day 180 the affected area had healed completely	Unlikely

Sponsor table 2.7.4-16, module 2

In TT02, 20 SAEs were reported and 9 were considered as associated or possibly so with Totect. All nine resolved during the study. There were 6 fever events, and four infections in the area of the extravasation and biopsies. One patient experienced somnolence and dizziness following the

first and second Totect infusions and was then removed from further Totect therapy (see section 7.1.3). See table below.

Table 14: Summary of SAEs in TT02

Patient number	Description	SOC/Preferred Term (MedDRA)	Outcome	Relationship
020301	Arrhythmia & intermittent hypokalemia	Cardiac disorders/arrhythmia Metabolism and nutrition disorders/hypokalemia	Resolved	Not related
	Respiratory insufficiency due to Aspergillus infection	Infections and infestations/bronchopulmonary aspergillosis	Death	Not related
020801	Septic shock due to neutropenia fever	Blood and lymphatic system disorders/febrile neutropenia Infections and infestations/septic shock	Death	Not related
023201	Fever	General disorders and administration site conditions/pyrexia	Resolved with sequelae	Suspected
023302	Somnolence and dizziness	Neurological disorders NEC/dizziness General disorders and administration site conditions/somnolence	Resolved	Suspected
024202	Pneumonia	Respiratory, thoracic and mediastinal disorders/ pneumonia	Death	Not related
024203	Pneumonia	Respiratory, thoracic and mediastinal disorders/ pneumonia	Resolved with sequelae	Not related
	Coma	Nervous system disorders/coma	Resolved with sequelae	Not related
	Pulmonary Aspergillus infection	Infections and infestations/systemic mycosis	Resolved	Not related
	Renal insufficiency	Renal and urinary disorders/renal failure	Ongoing	Not related
024204	Dizziness	Nervous system disorders/dizziness	Resolved with sequelae	Unlikely
024302	S. aureus infection at biopsy site	Infections and infestations/ neutropenic infection	Resolved	Probably
	Neutropenia with infection	Infections and infestations/ postoperative infection	Resolved	Suspected
024304	Diarrhea	Gastrointestinal disorders/diarrhea	Resolved	Suspected
	Fever	General disorders and administration site conditions/ pyrexia	Resolved	Suspected
	Suspected infection at biopsy area	Infections and infestations/postoperative infection	Resolved	Suspected
024305	Infection - stomatitis	Gastrointestinal disorders/stomatitis	Resolved	Suspected

	Infection at biopsy area	Infections and infestations/postoperative infection	Resolved	Not related
024306	Stomatitis	Gastrointestinal disorders/stomatitis	Resolved	Suspected
	Infection at biopsy area	Infections and infestations/postoperative infection	Resolved	Not related
024601	Diarrhea Fever	Gastrointestinal disorders/diarrhea General disorders and administration site conditions/ pyrexia	Resolved	Unlikely
024802	Dizziness Nausea Shortness of breath Fatigue	Nervous system disorders/dizziness Gastrointestinal disorders/nausea Respiratory, thoracic and mediastinal disorders/dyspnea General disorders and administration site conditions/fatigue	Resolved	Not related
	Infection in right arm at extravasation area	Infections and infestations/postoperative infection	Resolved with sequelae	Suspected
	Fever	General disorders and administration site conditions/pyrexia	Resolved	Suspected
024805	Hyperglycemia	Metabolism and nutrition disorders/hyperglycemia	Resolved	Not related
	Febrile neutropenia	Blood and lymphatic system disorders/febrile neutropenia	Resolved	Not related
024806	Pneumonia	Respiratory, thoracic and mediastinal disorders/ pneumonia	Resolved	Not related
024807	Fever without leukopenia	General disorders and administration site conditions/pyrexia	Resolved	Unlikely
024901	Febrilia (*sic*)	General disorders and administration site conditions/pyrexia	Ongoing	Not related
	Ascites	Gastrointestinal disorders/ascites	Ongoing	Unlikely
	Low appetite	Metabolism and nutrition disorders/decreased appetite	Resolved	Suspected
	[disease progression]	General system disorders NEC/disease progression		Not related
024903	Pneumonia	Respiratory, thoracic and mediastinal disorders/ pneumonia	Resolved	Probably
025401	Thrombosis in leg	Vascular disorders/thrombophlebitis	Resolved	Unlikely
025402	Fever	General disorders and administration site conditions/pyrexia	Resolved	Not related

Sponsor table 2.7.4-17, module 2

Reviewer comment: The SAEs reported in TT01 and TT02 are not unusual or notable for a population of patients with cancer receiving chemotherapy, and they are not suggestive of excessive or unusual Dex toxicity in this setting.

7.1.5 Common Adverse Events

Adverse events (AEs) were reported separately for each study and combined here for analysis.

Table 15: Adverse events (all causalities) by MeDRA in TT01 and TT02

MedDRA System Organ Class (SOC)	Patients N (%)		
	TT01 N = 23	TT02 N = 57	TT01 & TT02 combined N = 80
Total number of subjects with at least one event	23 (100%)	45 (78.9%)	68 (85.0%)
General disorders and administration site conditions	20 (87.0%)	26 (45.6%)	46 (57.5%)
Gastrointestinal disorders	15 (65.2%)	29 (50.9%)	44 (55.0%)
Infections and infestations	8 (34.8%)	16 (28.1%)	24 (30.0%)
Nervous system disorders	5 (21.7%)	14 (24.6%)	19 (23.8%)
Skin and subcutaneous disorders	4 (17.4%)	10 (17.5%)	14 (17.5%)
Respiratory, thoracic and mediastinal disorders	6 (26.1%)	7 (12.3%)	13 (16.3%)
Vascular disorders	5 (21.7%)	7 (12.3%)	12 (15.0%)
Blood and lymphatic system disorders	[6] (26.1%)	5 (8.8%)	11 (13.8%)
Psychiatric disorders	5 (21.7%)	6 (10.5%)	11 (13.8%)
Injury, poisoning and procedural complications	4 (17.4%)	6 (10.5%)	10 (12.5%)
Musculoskeletal and connective tissue disorders	3 (13.0%)	7 (12.3%)	10 (12.5%)
Metabolism and nutrition disorders	3 (13.0%)	5 (8.8%)	8 (10.0%)
Cardiac disorders	0	4 (7.0%)	4 (5.0%)
Eye disorders	1 (4.3%)	2 (3.5%)	3 (3.8%)
Investigations	0	2 (3.5%)	2 (2.5%)
Renal and urinary disorders	0	2 (2.0%)	2 (2.5%)
Reproductive system and breast disorders	2 (8.7%)	0	2 (2.5%)
General system disorders NEC	0	1 (1.8%)	1 (1.3%)
Immune system disorders	0	1 (1.8%)	1 (1.3%)
Neoplasms benign, malignant and unspecified	0	1 (1.8%)	1 (1.3%)
Neurological disorders NEC	0	1 (1.8%)	1 (1.3%)
Adverse events (AE) shows in [] for TT01 were MedDRA coded but were not included in the summary of clinical AEs by CTC as they were hematological toxicities and hence captured as laboratory-test-based AEs by CTC. Table shows number of patients with events within each SOC			

Sponsor table 2.7.4-5, module 2

Reviewer comment: These AEs likely primarily reflect the patients' underlying diseases and chemotherapy independent of the Totect.

Table 16: Summary of Clinical AEs by CTC (all causalities) in TT01 and TT02 combined with a 5% or greater incidence

CTC term	Unknown	Grade 1	Grade 2	Grade 3	Grade 4	All
Cardiovascular (general)						
Edema		8 (10.0%)	4 (5.0%)			12 (15.0%)
Phlebitis (superficial)		2 (2.5%)	5 (6.3%)	1 (1.3%)		8 (10.0%)
Constitutional						
Fever (in the absence of neutropenia, where neutropenia is defined as ANC < 1.0 x10^9/L)		7 (8.8%)	4 (5.0%)	4 (5.0%)		15 (18.8%)
Fatigue		2 (2.5%)	7 (8.8%)		1 (1.3%)	10 (12.5%)
Dermatology/skin						
Injection site reaction		14 (17.5%)	8 (10.0%)	1 (1.3%)		23 (28.8%)
Wound-infectious		2 (2.5%)	5 (6.3%)	7 (8.8%)		14 (17.5%)
Alopecia		2 (2.5%)	9 (11.3%)			11 (13.8%)
Gastrointestinal						
Nausea		22 (27.5%)	10 (12.5%)	1 (1.3%)	1 (1.3%)	34 (42.5%)
Vomiting		7 (8.8%)	7 (8.8%)		1 (1.3%)	15 (18.8%)
Diarrhea		5 (6.3%)	2 (2.5%)	2 (2.5%)		9 (11.3%)
Stomatitis/pharyngitis (oral/pharyngeal)		1 (1.3%)	5 (6.3%)	2 (2.5%)		8 (10.0%)
Anorexia		3 (3.8%)	2 (2.5%)			5 (6.3%)
Constipation	1 (1.3%)	2 (2.5%)	2 (2.5%)			5 (6.3%)
Mouth dryness		3 (3.8%)	1 (1.3%)			4 (5.0%)
Infection/febrile neutropenia						
Infection without neutropenia		2 (2.5%)	4 (5.0%)	1 (1.3%)		7 (8.8%)
Febrile neutropenia	1 (1.3%)	1 (1.3%)	1 (1.3%)	2 (2.5%)		5 (6.3%)
Neurological						
Dizziness/light-headedness	1 (1.3%)	4 (5.0%)	1 (1.3%)	2 (2.5%)		8 (10.0%)
Mood alteration-depression		1 (1.3%)	3 (3.8%)	2 (2.5%)		6 (7.5%)
Insomnia		2 (2.5%)	2 (2.5%)			4 (5.0%)
Neurology-Other		2 (2.5%)	1 (1.3%)	1 (1.3%)		4 (5.0%)
Pain						
Pain-Other		4 (5.0%)	5 (6.3%)			9 (11.3%)
Abdominal pain or cramping		3 (3.8%)	4 (5.0%)			7 (8.8%)
Headache		4 (5.0%)	1 (1.3%)			5 (6.3%)
Arthralgia		2 (2.5%)	1 (1.3%)	1 (1.3%)		4 (5.0%)
Pulmonary						
Dyspnea		4 (5.0%)	2 (2.5%)			6 (7.5%)
Pneumonitis/pulmonary infiltrates	1 (1.3%)	1 (1.3%)	2 (2.5%)	1 (1.3%)	1 (1.3%)	6 (7.5%)
Cough		3 (3.8%)	1 (1.3%)	1 (1.3%)		4 (5.0%)

Sponsor table 2.7.4-9, module 2

Reviewer comment: The effects possibly attributable to Totect are uncertain due to the combined effects of the patients' underlying diseases and chemotherapy

7.1.5.1 Eliciting adverse events data in the development program

AEs primarily reflect the underlying population and chemotherapy.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Clinical adverse events (AEs) and laboratory AEs were recorded on case report forms (CRFs) using NCI CTC version 2 definitions consistent with oncology reporting.

7.1.5.3 Incidence of common adverse events

See 7.1.5

7.1.5.4 Common adverse event tables

See 7.1.5

7.1.5.5 Identifying common and drug-related adverse events

See issues discussed above.

7.1.5.6 Additional analyses and explorations

See literature review of Dex AEs.

7.1.6 Less Common Adverse Events

See above.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology and chemistry studies were performed in a usual fashion for an oncology population. Attribution to Totect is uncertain as discussed above. Results for TT02 are shown below (TT01 results are similar but in fewer patients.) Day 0 in these tables indicates the first day of Totect treatment. In each table, results for all patients are shown for various time intervals before and after the extravasation event and the Totect therapy based on followup visit intervals. The number of patients available at each time interval is shown in the center of each table.

Table 17: Summary of serial neutrophil counts (mean) in the Totect treatment cycle –TT02

Day		n	WBC x10^9/L	
From	To		Mean	SD
-5	0	50	5,62	4,58
1	4	10	4,46	2,21
5	9	41	4,21	4,31
10	16	42	2,52	3,34
17	24	36	4,36	4,31
25	34	39	6,58	9,49
35	150	7	3,21	1,26

Sponsor table 2.7.4-19

Table 18: Summary of serial platelet count changes (mean) in the Totect treatment cycle –TT02

Day		n	x10^9/L	
From	To		Mean	SD
-5	0	57	312,60	139,34
1	4	13	267,69	147,27
5	9	49	185,20	109,43
10	16	52	167,80	99,40
17	24	43	417,26	182,06
25	34	46	315,47	160,38
35	150	9	288,39	50,46

Sponsor table 2.7.4-20, module 2

Table 19: Summary of mean serial ALT changes in the Totect treatment cycle –TT02

Day		n	U/L	
From	To		Mean	SD
-5	0	42	31,04	24,58
1	4	9	59,44	56,52
5	9	39	59,44	49,70
10	16	37	31,57	17,54
17	24	29	23,89	10,11
25	34	33	27,82	13,82
35	150	7	44,64	37,38

Sponsor table 2.7.4-22, module 2

Table 20: Summary of mean serial AST changes in the Totect treatment cycle –TT02

Day		n	U/L	
From	To		Mean	SD
-5	0	28	32,83	20,42
1	4	6	45,00	15,23
5	9	25	73,60	42,20
10	16	23	36,70	39,80
17	24	17	23,08	9,94
25	34	19	31,46	22,73
35	150	4	37,25	43,45

Sponsor table 2.7.4-24, module 2

Table 21: Number of patients with CTC grade 2, 3 or 4 laboratory toxicities in TT02

	CTC grade 2		CTC grade 3		CTC grade 4		CTC grade 2-4	
	N	%	N	%	N	%	N	%
Decreased WBC	17	29.8%	13	22.8%	11	19.3%	41	71.9%
Decreased neutrophils	11	19.3%	12	21.1%	11	19.3%	34	59.6%
Decreased hemoglobin	23	40.4%	2	3.5%			25	43.9%
Decreased platelets	3	5.3%	13	22.8%			16	28.1%
Increased ALT	11	19.3%	1	1.8%	4	7.0%	16	28.1%
Increased AST	14	24.6%	1	1.8%	1	1.8%	16	28.1%
Increased creatinine	6	10.5%	1	1.8%	1	1.8%	8	14.0%
Increased bilirubin	5	8.8%	1	1.8%			6	10.5%
Decreased calcium (total)	2	3.5%	1	1.8%	1	1.8%	4	7.0%
Decreased sodium			2	3.5%	1	1.8%	3	5.3%
Increased alkaline phosphatase	2	3.5%					2	3.5%
Increased calcium (total)					1	1.8%	1	1.8%
Decreased potassium			1	1.8%			1	1.8%
Increased potassium	1	1.8%					1	1.8%

Sponsor's table 12.7-14, module 5

Reviewer comment: The modest reductions in blood counts observed through the treatment cycle are consistent with the chemotherapy given and not suggestive of an important additive myelotoxicity from the addition of Totect. The approximate doubling of the AST and ALT are unusual for chemotherapy effects and likely reflect the Totect therapy. By the end of the cycle, these had returned to baseline in all patients. No other lab findings were abnormal during the Totect treatment period. Increased myelosuppression is described in the Zinecard label when used in combination with chemotherapy. However, no clear relationship with transaminase changes was observed when zinecard was combined with chemotherapy in patients with metastatic breast cancer. Please see the Zinecard label for further comments on the combination of dexrazoxane with chemotherapy including doxorubicin.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

No control group was included.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable due to study design.

7.1.7.4 Additional analyses and explorations

Not applicable. No clinical syndromes of toxicity were found.

7.1.7.5 Special assessments

Not applicable

7.1.8 Vital Signs

No relevant trends were observed.

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were assessed according to routine clinical care. No unexpected or informative deviations were reported.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No control group was included.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.4 Additional analyses and explorations

Lab changes were considered in light of historical experiences with Dex as a single agent. No noteworthy differences were observed.

7.1.9 Electrocardiograms (ECGs)

Not applicable

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not performed

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No control group was included.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable

7.1.9.4 Additional analyses and explorations

Not applicable

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

Not studied for this NDA

7.1.12 Special Safety Studies

None were performed

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None observed

7.1.14 Human Reproduction and Pregnancy Data

Not performed for this NDA and not applicable

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

None observed

7.1.17 Postmarketing Experience

None for this indication

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety population comprised 80 patients total in the two studies. All patients were to receive Dex 1000 mg/m2 IV within 6 hours of the event and again 1 day later, followed by 500 mg/m2 on the third day. When patients' biopsy results were reported as negative for fluorescence, they did not receive further Dex doses. External literature review provided the other sources for descriptions of Dex AEs and tolerance.

7.2.1.1 Study type and design/patient enumeration

This is provided in section 6.1.4

7.2.1.2 Demographics

This is provided in section 6.1.4, where it provides context for the efficacy analysis.

7.2.1.3 Extent of exposure (dose/duration)

Exposure was calculated by the reviewers from the reported dose given to each patient on each date of treatment divided by the patient's body surface area, as recorded, to compare the planned dosage with that actually administered. Exposure by day of therapy was provided by the applicant. See below.

Table 22: Reviewer table - Exposure as a function of intended dose, combined TT01 and TT02

Day	Planned dose	Number of patients	Mean dose administered
0 (event day)	1000 mg/m2	80	996.7 mg/m2
1	1000 mg/m2	72	994.9 mg/m2
2	500 mg/m2	69	499.9 mg/m2

Table 23: Exposure by day of therapy

	TT01 (N = 23)	TT02 N=57
Day 0	23 (100%)	57 (100%)
Day 1	19 (82.6%)	53 (93.0%)
Day 2	18 (78.3%)	51 (89.5%)
Day 3	0	1 (1.8%)
Day 4	0	1 (1.8%)

Sponsor table 2.7.4-1, module 2

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

7.2.2.1 Other studies

None performed for this application

7.2.2.2 Postmarketing experience

As described above, there is single agent data for Dex from earlier studies and also data for the combination of Dex with anthracycline treatment regimens.

7.2.2.3 Literature

The applicant's literature review included the applicant's work and that of alternative treatment methods for the event. No other therapy has demonstrated a clinically meaningful effect on the event.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is limited as noted above, reflecting the infrequency of the event and lack of contemporaneous controls. The dose and exposure appears adequate to assess the safety of the addition of Totect in this setting.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see the pharm-tox review by Dr McGuinn.

7.2.5 Adequacy of Routine Clinical Testing

Routine testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not studied.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant sought AEs in a standard and consistent manner. The lack of an internal control limits the inferences possible.

7.2.8 Assessment of Quality and Completeness of Data

The only additional internal control possible might be to compare AEs observed for the prior or subsequent chemotherapy cycle with the cycle in which Totect was given. The applicant has been asked to provide this analysis. Audit by the Division of scientific investigation did not identify any problems with the data as assessed at the two major enrolling sites in Denmark.

7.2.9 Additional Submissions, Including Safety Update

A 120 day safety update report was received June 2, 2006, letter date May 31, 2006. TopoTarget A/S advises that there is no new safety information. The applicant was asked to provide safety information for the following or preceding chemotherapy treatment cycle (without Totect) to compare with the Totect cycle, but the applicant did not provide this information.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As described above, the AEs reported by the applicant are unlikely to reflect the effects of Totect. Dexrazoxane AEs are described in section 2.6 based on review of literature published 20 or more years ago.

7.4 General Methodology

As noted above, the submitted studies do not isolate the adverse effects of Totect, and these can only be approximated from external literature review (see section 2.6).

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Tables 13 and 14 provide the pooled AE data.

7.4.1.1 Pooled data vs. individual study data

The individual study data and the pooled data are consistent.

7.4.1.2 Combining data

Data has been combined for safety and efficacy analysis.

7.4.2 Explorations for Predictive Factors

Not possible with the data available.

7.4.2.1 Explorations for dose dependency for adverse findings

Not possible. Only one dose was used, and patients received almost 100% of the planned doses.

7.4.2.2 Explorations for time dependency for adverse findings

No late AEs were observed which could plausibly be related to Totect. Late sequelae of the therapy represent more the toxicity of the chemotherapy and not the effects of Totect treatment.

7.4.2.3 Explorations for drug-demographic interactions

None were evident in these small studies.

7.4.2.4 Explorations for drug-disease interactions

None were evident in these small studies.

7.4.2.5 Explorations for drug-drug interactions

None were observed.

7.4.3 Causality Determination

In this reviewer's opinion, the only AEs plausibly associated with the Totect were:

1. Observations of pain on infusion of Totect and
2. Transient elevations of AST and ALT enzymes peaking about 10-14 days following Totect and resolved by 4 weeks' time

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant's dosing regimen appears highly effective. The Totect treatment protocol consists of Totect 1000 mg/m2 IV given as soon as possible and within 6 hours of an extravasation on the day of the event, and the same dose is repeated the next day. On the third day 500 mg/m2 IV is given. No particular dose-toxicity concerns were identified. Dose modifications for special populations could not be estimated from the safety population included. No dose-response information is available. The submitted information does not allow inferences to be made regarding alternative dose or schedules of Totect.

8.2 Drug-Drug Interactions

No drug interactions were observed in the two studies.

8.3 Special Populations

Study eligibility was limited to patients age 18 and over. Pregnant and nursing women were excluded. Patients also were to be excluded for AST (or ALT), bilirubin, LDH, or alkaline phosphatase > 3 times ULN. Most patients had normal baseline chemistries and serum creatinine before receiving Totect.

8.4 Pediatrics

The studies were conducted in adult oncology departments, and protocol eligibility was limited to ages 18 and over. No pediatric patients were studied although children may be at risk for this event.

8.5 Advisory Committee Meeting - Consultants

The NDA was not presented to ODAC. The external consultant, Dr. Libutti, provided the following advice via tcon. First, the event is decidedly less common in the U.S. because of the general use of CVADs. Sequelae mostly reflect the location of the event and the quantity of anthracycline infiltrated. Blistering tends to be a later symptom but does indicate increased severity and need for surgery. No guidelines exist for determining the timing or extent of surgery. Even after surgery, serious permanent morbidity may remain. If this product can reduce the consequences of extravasation with low toxicity, it would represent an advance which would likely be widely adopted. Additional supportive animal data, such as a minipig skin model, might provide further verification.

8.6 Literature Review

See section 2.6 for literature review pertaining to background and event information.

8.7 Postmarketing Risk Management Plan

No plan has been requested of or submitted by the applicant. The overall risk for Totect is judged to be low.

8.8 Other Relevant Materials

This reviewer has concerns about the proprietary name Totect being confused with Topotecan.

9 OVERALL ASSESSMENT

9.1 Conclusions

The medical reviewer concurs with the applicant's findings on the efficacy and safety of Totect for the reduction of anthracycline extravasation tissue injury such that surgical intervention is not usually necessary. There is substantial uncertainty about the frequency with which serious

extravasations (those leading to tissue necrosis and or ongoing symptoms requiring surgical intervention) occur. However, the studies conducted appear to reflect a carefully monitored adult patient population receiving anthracycline chemotherapy in a typical fashion, and the frequency of required surgical intervention for extravasation injury in the absence of Totect may be assumed to be above the 2% frequency incurred with Totect therapy. In a recent, although retrospective experience from the MD Anderson hospital, among 12 doxorubicin extravasations, the majority required surgery.[1] The incidence of an extravasation event in current U.S. practice has been declining and is low, due to the general use of CVADs and the availability of specialized nurses who are attentive to this concern.

When an extravasation is judged to be likely, no tissue biopsy appears to be necessary to guide use of Totect, given its relative safety. If the event is uncertain, a first dose of Totect could be given while an attempt is made to assess tissue fluorescence as described by the applicant. Treatment should not be withheld beyond 6 hours if the tissue examination will be delayed. While it would be desirable to know if lesser amounts of Totect could be similarly efficacious, this would be difficult to study given the infrequency of the event and possible risk of reduced efficacy.

While some interference with the therapeutic activity of the anthracycline may occur in the treatment cycle in which the Totect is given, this concern is not important in comparison with the desirability of protection from extravasation injury.

9.2 Recommendation on Regulatory Action

I recommend regular approval for Totect for the indication, treatment of suspected extravasation during anthracycline chemotherapy administration, following satisfactory resolution of deficiencies in CMC and microbiology. Please see section 1.1

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

See section 1.2.1

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

See section 1.2.3

9.4 Labeling Review

Please see section 10.2.

9.5 Comments to Applicant

The concerns expressed in Section 1.2 and the remaining CMC and microbiology deficiencies have been communicated to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Individual study reports are provided in the efficacy and safety sections, respectively.

10.2 Line-by-Line Labeling Review

A line-by-line review was conducted. A draft label revision was sent to the applicant and a reply has been received. Further labeling will follow the resolution of the pending deficiencies.

REFERENCES

[1] Langstein HN, Duman H, Seelig D, Butler CE, Evans GRD. Retrospective study of the management of chemotherapeutic extravasation injury. Ann Plastic Surg 2002; 49:369-374.

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[4] Natale RB, Wheeler RH, Liepman MK et al: Phase II Trial of ICRF-187 in non-small cell lung cancer. Cancer Treat Rep 1983; 67:311-313.

[5] Venturini M, Michelotti A, Del Mastro L et al. J Clin Oncol. 1996; 14:3112-20.

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7/18/2006 05:24:59 PM
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7/20/2006 09:13:33 AM
BIOMETRICS

Rajeshwari Sridhara
7/20/2006 09:17:01 AM
BIOMETRICS
Rigorous statistical analysis could not be conducted because of the limited data submitted in this application. The recommendations are based on clinical review and judgement.

Ramzi Dagher
7/20/2006 09:25:50 AM
MEDICAL OFFICER