CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-025

SUMMARY REVIEW

Division Director Summary Review of an NDA Resubmission

NDA: 22-025
Drug: Totect™ (dexrzoxane hydrochloride) for Injection
Applicant: TopoTarget A/S
Date: May 24, 2007

This 505(b)(2) application seeks approval of Totect "for the treatment of extravasation resulting from IV anthracycline chemotherapy." For details on the original application see the Division Director Summary Review of a New Drug Application dated July 31, 2006. An approvable action was taken on August 1, 2006. The applicant was asked to address the following CMC and microbiology deficiencies:

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

[redacted] b(4)

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

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

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

6. [redacted] has responded that they do not provide certification that their stoppers are free of endotoxins. Please provide validation b(4)

data to demonstrate that the —— stoppers are processed so that they are free of bacterial endotoxins. b(4)

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

——————————————————————————— b(4)

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

The applicant submitted a complete response to the approvable letter on November 24, 2006. This memo will summarize the reviews of the complete response.

Chemistry Review

The Chemistry Review of the resubmission by Leon Epps, Ph.D. was completed on May 22, 2007. The review made the following recommendation and conclusion on approvability: "From a Chemistry, Manufacturing and Controls standpoint, this new Drug Application is approvable pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert, and upon an acceptable recommendation from the Office of Compliance regarding cGMP compliance."

Chemistry Branch Chief Memo

The memo by Ravi S. Harapanhalli, Ph.D. was completed on May 24, 2007. Dr. Harapanhalli made the following recommendations.

The Office of Compliance recommended "withhold" for this NDA on May 23, 2007. Pharma Hameln site was deemed out of compliance during a recent inspection. Pharma Hameln was listed as the primary manufacturing site for the ——————————————— Ben Venue Laboratory was also listed as an alternative manufacturing site and was deemed acceptable for GMP compliance. The withhold recommendation for the primary b(4)

manufacturing site is a serious concern and hence from CMC perspective, we will recommend 'approvable" for this NDA. The following deficiency needs to be included in the action letter:

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

Carton and Container labels:

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

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

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

Product Quality Microbiology Review

The microbiology review of the resubmission was completed by Anastasia G. Lolas on April 5, 2007. The review recommended that the application be approved.

Clinical Review

No new clinical data was submitted. A memo dated May 3, 2007 by Robert Kane, M.D., noted that labeling discussions with the sponsor have been completed with agreement reached on the labeling on May 1, 2007.

Clinical Pharmacology and Biopharmaceutics

A second Clinical Pharmacology and Biopharmaceutics review by Gene Williams, Ph.D. dated May 11, 2007 stated that the NDA is acceptable from a clinical pharmacology and biopharmaceutics perspective and recommended the following Phase 4 study commitment:

The Applicant should commit to completing and submitting to the FDA the population pharmacokinetic analysis they have previously agreed to. This analysis

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

The applicant agreed to this commitment on March 9, 2007.

DMETS Consults

A re-review of the proprietary name was completed by DMETS on May 15, 2007. DMETS had no objection to the proposed name and noted that DDMAC finds the name acceptable from a promotional perspective.

A DMETS consult on the labels and labeling was completed on March 7, 2007. DMETS made a number of recommendations which were addressed during the labeling negotiations.

Conclusion

The application is approvable. Before the application may be approved, the CMC deficiencies in Dr. Harapanhalli's memo must be corrected.

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

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

/s/

Robert Justice
5/25/2007 01:53:26 PM
MEDICAL OFFICER
The review was completed on 5/24/07 but DFS was down.

Division Director Summary Review of a New Drug Application

NDA: 22-025
Drug: Totect™ Powder and Solvent for Injection (dexrazoxane as hydrochloride)
Applicant: TopoTarget A/S
Date: July 31, 2006

This 505(b)(2) application seeks approval of the following indication: "Totect™ is indicated for the treatment of anthracycline extravasation during chemotherapy." The reference drug is Zinecard® (dexrazoxane for injection). The mechanism by which Totect™ ameliorates tissue damage resulting from the extravasation of anthracycline drugs is unknown. Some evidence suggests that dexrazoxane inhibits topoisomerase II reversibly. The clinical efficacy and safety data are summarized in the following excerpts from the FDA's draft labeling which was sent to the company on July 12, 2006.

> Totect™ (dexrazoxane) was studied in two similar, open-label, single arm, multi-center studies testing whether Totect administration could reduce or avoid surgical intervention for tissue injury following anthracycline extravasation.
>
> In the two studies, patients who were receiving single-agent anthracycline chemotherapy intravenously and who developed symptoms of pain, burning, swelling, and/or redness near the infusion site were eligible. Skin biopsy samples from the suspected skin area were examined for the presence of anthracycline as determined by the presence of tissue fluorescence; however, therapy was not delayed for this test result.
>
> In both studies, treatment with Totect™ was to begin as soon as possible and no later than 6 hours after extravasation with retreatment 24 and 48 hours later (a total of 3 doses). Totect was administered as 1-2 hour IV infusions. The first and second doses were 1000 mg/m^2 and the third dose was 500 mg/m^2. No dose modifications were planned except for patients whose body surface area exceeded 2 m^2, in which case the total daily dose limit on the first and second day was 2000 mg/day and 1000 mg on the third day.
>
> Demographics in the two studies were similar. Both enrolled men and women. Median age was 57 years in Study 1 (range 41-76) and 55 years in Study 2 (range 34-81). In studies 1 and 2 the anthracyclines most commonly associated with extravasation in the evaluable patients were doxorubicin (39% and 44% respectively) and epirubicin (61% and 56% respectively). Two patients were receiving daunorubicin. Peripheral IV sites of extravasation included the forearm in 63%, the hand in 21%, and the antecubital area in 11%; four patients (5%) received the anthracycline via a central venous access device (CVAD). Most patients in studies 1 and 2 presented with swelling (89% and 81% respectively),

redness (78% in both studies), and pain (39% and 44% respectively). In study 1, 11% also presented with blisters. The median baseline lesion area was 24 cm^2 (1-75) in study 1 and 25 cm^2 (1-253) in study 2.

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

In study 1, none of the 19 evaluable patients required surgical intervention and none had serious late sequelae.

In study 2, one of the 38 evaluable patients required surgery. One additional patient of the 57 enrolled, who was judged not evaluable because of protocol violations, also required surgery for tissue necrosis. Of 13 patients reporting late sequelae at the event site, all were judged as mild sequelae except in the one patient who required surgery.

None of the 4 patients with CVADs required surgical intervention.

In the two clinical studies, Totect™ was administered to patients also receiving chemotherapeutic agents for cancer, and the adverse event profile reflects the combination of Totect, underlying disease, and chemotherapy. The adverse event data reflect exposure to Totect™ in 80 patients who received the first dose, 72 patients who received two doses, and 69 patients who received all three doses. Table 1 summarizes adverse events occurring with ≥ 5% frequency.

Table 1 Adverse Events Occurring at ≥ 5% Frequency

MedDRA System Organ Class (SOC) and Preferred term	Study 1 and 2 Combined (All causalities) N=80 (%)
Total number of patients with at least one event	68 (85)
General disorders and administration site conditions	46 (58)
Pyrexia	17 (21)
Injection site pain	13 (16)
Fatigue	10 (13)
Edema peripheral	8 (10)
Injection site phlebitis	5 (6)

MedDRA System Organ Class (SOC) and Preferred term	Study 1 and 2 Combined (All causalities) N=80 (%)
Gastrointestinal disorders	44 (55)
Nausea	34 (43)
Vomiting	15 (19)
Diarrhea	9 (11)
Abdominal pain	5 (6)
Constipation	5 (6
Infections and infestations	24 (30)
Postoperative infection	13 (16)
Nervous system disorders	19 (24)
Dizziness	9 (11)
Headache	5 (6)
Skin and subcutaneous disorders	14 (18)
Alopecia	11 (14)
Respiratory, thoracic and mediastinal disorders	13 (16)
Dyspnea	6 (8)
Pneumonia	5 (6)
Cough	4 (5)
Vascular disorders	12 (15)
Blood and lymphatic system disorders	11 (14)
Anemia	5 (6)
Psychiatric disorders	11 (14)
Depression	6 (8)
Insomnia	4 (5)
Musculoskeletal and connective tissue disorders	10 (13)
Metabolism and nutrition disorders	8 (10)
Anorexia	4 (5)
Cardiac disorders	4 (5)

Neutropenia and febrile neutropenia each occurred in 2.5% of patients.

Table 2 summarizes laboratory adverse events from studies 1 and 2 combined.

Table2: Laboratory Adverse Events

CTCAE version 3 Term	CTC grade 3	CTC grade 4	CTC grade 2 to 4
	N (%)	N (%)	N (%)
Hematologic:			
Decreased hemoglobin	2 (3)	0	34 (43)
Decreased WBC	20 (25)	16 (20)	58 (73)
Decreased neutrophils	17 (22)	19 (24)	48 (61)
Decreased platelets	17 (21)	0	21 (26)
Hepatic:			
Increased bilirubin	1 (2)	0	6 (11)
Increased AST	1 (1)	1 (1)	21 (28)
Increased ALT	1 (1)	4 (5)	17 (22)
Increased alkaline phosphatase	0	0	3 (4)
Increased LDH	0	0	1 (5)
Metabolic:			
Increased creatinine	1 (2)	1 (2)	8 (14)
Decreased sodium	4 (5)	1 (1)	5 (6)
Increased calcium total	1 (2)	1 (2)	4 (7)

Clinical and Statistical Review

The combined Clinical and Statistical Review was completed on July 17, 2006. The review made the following 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.

The review recommended the following 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.

Although there were no required phase 4 commitments, the review recommended the following Phase 4 request.

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.

Clinical Inspection Summary

The Division of Scientific Investigations inspected 4 of the 10 study sites. The overall assessment of findings and general recommendations are summarized below.

The study data collected by [redacted] b(4)
appear reliable.

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

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

Clinical Pharmacology and Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics Review by Gene Williams, Ph.D. stated that "This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective." The review recommended a Phase 4 commitment to complete and submit to the FDA the Applicant's planned study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

DMETS Consultation

The DMETS consultation of July 18, 2006 had the following recommendations.

1. DMETS has no objections to the use of the proprietary name, Totect. This is considered a final decision. However, if approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Totect acceptable from a promotional perspective.

Chemistry Reviews

The Chemistry Review by Leon A Epps, Ph.D. stated that the NDA is approvable from a CMC perspective. The CMC deficiencies (including microbiology deficiencies) and additional comments are listed below.

1. Your amendment dated March 31, 2006 states that [redacted] would not be ready for inspections until January, 2007. Since this facility carries out testing of the [redacted] and since this function is critical to the assurance of product quality, the facility is required to be inspected before approval of the NDA. Therefore, in your resubmission, provide a statement of readiness of this facility for inspections. b(4)

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

[redacted] b(4)

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

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

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

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

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

[redacted] b(4)

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

Additional Comments:

11. Provide stability updates with statistical analysis in the resubmission.

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

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

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

The CMC Branch Chief Memo by Ravi S. Harapanhalli, Ph.D. concurred that the NDA is approvable from a CMC perspective but did not include comment 11.

Product Quality Microbiology Review

The Product Quality Microbiology Review by Anastasia G. Lolas recommended an approvable action pending resolution of the microbiology deficiencies. The deficiencies and comments are listed below.

Microbiology deficiencies and questions remain even after the submission of the amendment. The manufacturing site for the lyophilized product will not be ready for inspection until January 2007. The filter retention study will not be complete until Quarter 4 of 2006. These facts alone pose uncertainty regarding the sterility assurance of the product. It is strongly recommended that [redacted] manufacturing sites are inspected by the Agency. b(4)

The following deficiencies need to be addressed by the applicant:

Lyophilized product:

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

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

3. (Communicated to the applicant on June 22, 2006) : [redacted] has responded that they do not provide certification that their stoppers are free of endotoxins. Please provide validation data to demonstrate that the [redacted] stoppers are processed so that they are free of bacterial endotoxins. b(4)

Solvent:

1. The applicant states in the amendment that the production temperature set-point for the sterilization of the solvent is [redacted] for [redacted] minutes ([redacted] minutes delay time). The container-closure integrity test data provided are valid for a temperature set-point of [redacted]) according to the applicant. There are inconsistencies regarding the temperature set-point of the sterilization cycle and additional clarification is needed. b(4)

[redacted] b(4)

[redacted] b(4)

3. Regarding the [redacted] provide the sampling method along with SOP 1QW0061. What is the % recovery of endotoxin? Has it been evaluated how much endotoxin is removed by the washing process? b(4)

The following comments should be provided to the applicant:

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

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

3. Regarding the applicant's comment about submitting updated SOPs and documents to the Agency: It is not necessary to submit the documents; however, they should be available for inspection.

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by W. David McGuinn, Jr., Ph.D., concluded that "The available Pharmacology and Toxicology information is adequate to support the approval of TOTECT™ for use in the proposed clinical indication." A number of labeling recommendations were provided.

Acting Deputy Director Summary Review of a New Drug Application

The Acting Deputy Director Summary Review of this NDA by Ann Farrell, M.D. concluded the following.

> Anthracycline extravasation is associated with serious irreversible morbidity. I agree with the conclusions of the review disciplines regarding the efficacy and safety of this product. The CMC and Microbiology disciplines identified deficiencies that must be addressed prior to approval including the need for inspection and sterility information. If it were not for the outstanding CMC and microbiology deficiencies, this application would be approved. However, the fact that the sterility cannot be assured and this product would be administered after myelosuppressive chemotherapy had been given increases the potential risk of a life-threatening infection, therefore this application is approvable. The

deficiencies and comments should be forwarded to the sponsor so these issues can be addressed.

Conclusions

I concur with the approvable recommendations. Although the clinical trials were single-arm studies, randomized controlled trials for this indication are not feasible. As stated by the reviewers, the efficacy demonstrated in the two submitted studies was sufficient to outweigh concerns about comparisons to historical controls. In addition, Totect did not appear to significantly increase the toxicity of chemotherapy. I do not believe that the Phase 4 suggestion for a registry is necessary but this will be reconsidered during the next review cycle. I also concur with DMET's conclusions regarding the proprietary name.

The application is approvable pending resolution of the CMC and microbiology deficiencies and agreement on labeling.

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

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/s/

Robert Justice
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MEDICAL OFFICER

Division of Drug Oncology Products
Acting Deputy Division Director Summary Review of a New Drug Application

NDA: 22-025
Drug: Totect (dexrazoxane hydrochloride)
Applicant: TopoTarget A/S
Date: July 27, 2006

This new drug application was received on February 1, 2006 for the following proposed indication: Totect is indicated for the treatment of anthracycline extravasation during chemotherapy.

The proposed dosing regimen is 1000 mg/m^2 given intravenously once daily for the first 2 days then 500 mg/m^2 given intravenously on the third day. The maximum dose to be administered daily is 2000mg corresponding to a dose of 1000 mg/m^2 for a patient with a body surface area of 2.0 m^2.

This application is approvable due to outstanding Chemistry, Manufacturing, and Control and Microbiology (CMC) issues as detailed below.

The CMC review team identified 10 deficiencies. The majority concerned lack of readiness for inspections and inability to resolve issues regarding inspection during the review cycle.

The following text regarding the Microbiology Deficiency is excerpted from the microbiology review:

The product specific filter bacterial retention study for the lyophilized product is not complete yet. There are inconsistencies and inadequate data to support the ——— sterilization of the solvent. The risk to the patient is high because without adequate sterilization validation data, the sterility of the product is not assured. b(4)

The CMC review team and microbiology reviewer had additional recommendations and comments for the sponsor. Please see these listed below.

Clinical Review
The Clinical Review was completed by Robert Kane, M.D. on July 20, 2006. Dr. Kane recommended regular approval after resolution of the CMC and microbiology deficiencies.

The following recommendation on regulatory action, summary of the clinical program, and efficacy and safety findings are excerpted from the Executive Summary of Dr. Kane's review:

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.

Summary
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, 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.

The following text is excerpted from Dr. Kane's Efficacy and Safety Summary.

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% 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.

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.

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 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.

Clinical Pharmacology Review

The Clinical Pharmacology Review was completed by Gene Williams, Ph.D. on July 24, 2006. The reviewer recommended approval and a Phase 4 commitment to complete and submit to the FDA the Applicant's planned study of the pharmacokinetics of dexrazoxane following the clinical dose regimen in patients with extravasation.

Pharmacology/Toxicology Review

The Pharmacology/Toxicology Review was completed by William D. McGuinn, Ph.D. on July 26, 2006. The review concluded that the product is approvable from pharmacology/toxicology point of view and there are no recommendations for additional studies.

Chemistry, Manufacturing and Controls (CMC) Review

The CMC Review was completed by Leon Epps, Ph.D. on July 26, 2006. The review concluded that the product is approvable. The following text is excerpted from the Branch Chief's review by Dr. Ravi S. Harapanhalli, Ph.D.

Unresolved inspectional issues:

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

- The [redacted] manufacturer [redacted] would be ready for inspection in 3 months. (Subsequently this site was inspected and deemed acceptable for cGMP compliance.) b(4)
- The [redacted] manufacturer [redacted] and the testing sites [redacted] b(4)

[redacted] Integrated Commercialization Solutions, USA were all listed as being ready for inspection. b(4)

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

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

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

[redacted] b(4)

b(4)

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

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

Unresolved issues with microbial product quality:

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

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

1. Your amendment dated March 31, 2006 states that [redacted] would not be ready for inspections until January, 2007. Since this facility carries out testing of the [redacted] and since this function is critical to the assurance of product quality, the facility is required to be inspected before approval of the NDA. Therefore, in your resubmission, provide a statement of readiness of this facility for inspections. b(4)

2. Your amendment dated March 17, 2006 stated that Integrated Commercialization Solutions, USA (ICS) was ready for inspections. However, as on May 4, 2006, this facility was not ready for inspections. Your subsequent e-mail correspondence dated July 19, 2006 suggested

that ICS was now ready for inspections, however, an official amendment stating readiness of this firm for inspection was not submitted. In your resubmission provide a statement of readiness of this facility for inspections.

[redacted] b(4)

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

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

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

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

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

9. [redacted] b(4)

b(4)

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

Additional Comments:

11. The floor plan diagrams should be updated to depict product flow to — lyophilizers instead of —(based on the sterilization validation data provided in the amendment, – lyophilizers are to be used for the product) and remove the ——————————————— b(4)
——————— The updated floor plans should be available for inspection.

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

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

Microbiology Review
The Product Quality Microbiology Review by Anastasia G. Lolas dated July 12, 2006, stated that the application could be approved after successful resolution of deficiencies.

The following is excerpted from the microbiology review:

1. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS
Microbiology deficiencies and questions remain even after the submission of the amendment. The manufacturing site for the lyophilized product will not be ready for inspection until January 2007. The filter retention study will not be complete until Quarter 4 of 2006. These facts alone pose uncertainty regarding the sterility assurance of the product. It is strongly recommended that ——————— b(4)
——————— manufacturing sites are inspected by the Agency.

The following deficiencies need to be addressed by the applicant:

Lyophilized product:
1. Regarding the microbiological environmental monitoring program, provide the growth media, incubation conditions, and actions taken when alert and action levels are exceeded. Identify the air samplers used.
2. The product-specific bacterial filter retention study should be submitted as soon as it is complete along with the flow rate and pressure parameters used during production.

3. (Communicated to the applicant on June 22, 2006) [redacted] has responded that they do not provide certification that their stoppers are free of endotoxins. Please provide validation data to demonstrate that the [redacted] stoppers are processed so that they are free of bacterial endotoxins. b(4)

Solvent:
1. The applicant states in the amendment that the production temperature set-point for the sterilization of the solvent is [redacted] for [redacted] minutes [redacted] minutes delay time). The container-closure integrity test data provided are valid for a temperature set-point of [redacted] according to the applicant. There are inconsistencies regarding the temperature set-point of the sterilization cycle and additional clarification is needed. b(4)

[redacted] b(4)

3. Regarding the pyroburden monitoring program of vials, provide the sampling method along with SOP 1QW0061. What is the % recovery of endotoxin? Has it been evaluated how much endotoxin is removed by the washing process?

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

The updated floor plans should be available for inspection.
2. A meeting or conference call can be arranged to discuss the media fill acceptance criterion.
3. Regarding the applicant's comment about submitting updated SOPs and documents to the Agency: It is not necessary to submit the documents; however, they should be available for inspection.

Division of Scientific Investigation
Field inspectors investigated 4 sites in Denmark and did not find any evidence of poor study conduct, unreliable data or other concerns. No 483 letters were issued as a result of the inspection.

Division of Medication Errors and Technical Support (DMETS)
The proprietary name review by DMETS/ODS was completed. DMETS had no objections to the use of the proprietary name, Totect, provided recommendations for label and labeling revisions, and found the name to be acceptable from a promotional perspective.

Division of Drug Marketing, Advertisement, and Communications (DDMAC)
DDMAC reviewer provided comments on the draft labeling for consideration during the labeling negotiations.

Conclusion
Anthracycline extravasation is associated with serious irreversible morbidity. I agree with the conclusions of the review disciplines regarding the efficacy and safety of this product. The CMC and Microbiology disciplines identified deficiencies that must be addressed prior to approval including the need for inspection and sterility information. If it were not for the outstanding CMC and microbiology deficiencies, this application would be approved. However, the fact that the sterility cannot be assured and this product would be administered after myelosuppressive chemotherapy had been given increases the potential risk of a life-threatening infection, therefore this application is approvable. The deficiencies and comments should be forwarded to the sponsor so these issues can be addressed.

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/s/

Ann Farrell
7/27/2006 09:33:17 AM
MEDICAL OFFICER