CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-025

PROPRIETARY NAME REVIEW(S)

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 17, 2006

NDA #: 22-025

NAME OF DRUG: **Totect™**
(Dexrazoxane HCl for Injection)
500 mg/vial

NDA SPONSOR: TopoTarget A/S

I. INTRODUCTION

This consult was written in response to a request from the Division of Drug Oncology Products, for an assessment of the proprietary name "Totect" regarding potential name confusion with other proprietary or established drug names. Draft labels and labeling were provided for review and comment.

PRODUCT INFORMATION

Totect is a 505(b)(2) drug product. Totect is indicated for the treatment of anthracycline extravasation during chemotherapy. Totect should be administered intravenously once daily for three consecutive days at the following recommended dose:

Recommended Dose	
Day 1	1000 mg/m^2
Day 2	1000 mg/m^2
Day 3	500 mg/m^2

Totect will be available as a powder and must be diluted with sodium lactate and then further diluted in 0.9% sodium chloride. The maximum dose to be administered is 2000 mg of dexrazoxane (corresponding to the dose in a patient with a 2 m^2 body surface area). The first infusion should be administered as soon as possible and within the first six hours after the incident. The indicated dose should be infused intravenously over 1 to 2 hours on day 1 and as a rapid drip infusion on days 2 and 3. Totect will be supplied in boxes containing 10 vials of 500 mg dexrazoxane and 10 vials of solvent for injection.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii,iv] for existing drug names which sound-alike or look-alike to "Totect" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of

[i] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2005, and the electronic online version of the FDA Orange Book.
[iv] Phonetic and Orthographic Computer Analysis (POCA)

the U.S. Patent and Trademark Office's Text and Image Database[i] and Clinical Pharmacology[ii] were also conducted. The Saegis[iii] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (two requisitions) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Totect. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Totect.

2. The Expert Panel identified nine (9) proprietary names that were thought to have potential for confusion with Totect. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Totect	Dexrazoxane HCl Powder for Injection: 500 mg/vial	Administer intravenously over 1-2 hours on day 1 and then as a rapid drip infusion on days 2 and 3. Day 1: 1000 mg/m^2 Day 2: 1000 mg/m^2 Day 3: 500 mg/m^2	
Tolectin Tolectin DS Tolectin 600	Tolmetin Sodium Tablets: 200 mg Capsules: 400 mg Tablets: 600 mg	Starting dose is 400 mg TID. Therapeutic range is from 600 mg to 1800 mg daily in divided doses (usually TID).	LA
Cytotec	Misoprostol Tablets: 100 mcg, 200 mcg	200 mcg four times a day, with food. Off-label use: Pregnancy termination: 400 mcg x 2 days	SA
Tobrex	Tobradex Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	Solution: 1-2 drops in affected (s) every 4 hours. Ointment: Apply a half-inch ribbon into the affected eye(s) every 3 -4 hours until improvement.	LA/SA
Sutent	Sunitinib Malate Capsules: 12.5 mg, 25 mg, 50 mg	50 mg once daily on a schedule of 4 weeks on treatment followed by 2 weeks off.	LA
Hycamtin	Topotecan Injectable: 4 mg/vial	Ovarian cancer and Small cell lung cancer: 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course.	LA

[i] WWW location http://www.uspto.gov.
[ii] Clinical Pharmacology, online version available at http://cpip.gsm.com
[iii] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Totect	Dexrazoxane HCl Powder for Injection: 500 mg/vial	Administer intravenously over 1-2 hours on day 1 and then as a rapid drip infusion on days 2 and 3. Day 1: 1000 mg/m^2 Day 2: 1000 mg/m^2 Day 3: 500 mg/m^2	
		Cervical cancer: 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on day 1, 2, and 3.	
Acutect	Technetium Tc-99 Apcitide Injection	Inject into an upper extremity at a dose of 100 mcg of bibapcitide radiolabeled with 20 mCi of technetium 99m.	LA
Kotex	Brand of feminine hygiene products.		SA
Totectin (foreign drug)	Australian drug product. De-worming drug product for horses.	No additional information	LA/SA
Totacef (foreign drug- Italy, Hungary, Israel)	Cefazolin Sodium 250 mg, 500 mg, 1 g	250 mg to 1 g of cefazolin every 6 to 12 hours administered by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion. Maximum daily dose is 6 g.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Totect with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Requisition prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Totect (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Requisition RX #1: 2332 | Totect 2 vials	Totect Dispense # 2 vials To General Surgery Clinic
Requisition RX #2: 2 | 2332 | Totect	

2. Results:

   None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Totect", the Expert Panel's primary concerns relating to look-alike and sound-alike confusion with Totect are Tolectin, Cytotec, Sutent, Tobrex, Topotecan, Acutect, and Kotex. In an independent search conducted by DMETS, we also identified Tolecef and Totectin as look-alike medications marketed in other countries.

Tolecef is a cefazolin medication marketed in Italy, Hungary, and Israel. Totectin is a de-worming drug product for horses that is marketed in Australia. Although Tolecef and Totectin may look similar to Totect, DMETS believes the actual possibility for confusion between these product names to be minimal due to the areas of marketing. Additionally, Kotex is the brand name of a feminine hygiene product line. Although Kotex has a phonetic similarity to Totect, the likelihood of Kotex being ordered on a prescription is minimal. In the unlikely event that Kotex is written on a prescription pad or in an inpatient setting, product characteristics such as strength, indication for use, frequency of administration, route of administration and dosage formulation will not be listed on the prescription, thus, confusion between Kotex and Totect is minimal. Therefore, Tolecef, Totectin, and Kotex will not be discussed further.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Totect.

1. Tolectin was identified as a name with a similar appearance to Totect when scripted. Tolectin, Tolectin DS, and Tolectin 600 are indicated for the treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). Tolectin is available as Tolectin, Tolectin DS, and Tolectin 600. Although Tolectin DS and Tolectin 600 are still marketed, it appears as though Tolectin is no longer marketed; however, a generic formulation is available. Thus, a practitioner could write for Tolectin and the patient would receive the generic equivalent. Therefore, we will still evaluate the similarity between this name pair.

   Tolectin and Totect share a similar beginning ("Tolect-" vs. "Totect"). However, Tolectin appears longer in length than Totect as it contains 8 letters whereas Totect contains only 6 letters. The ending of Tolectin ("-in") helps to elongate the name and distinguish it from Totect (see sample below). Tolectin and Totect share overlapping doses. For example a patient with a BSA of 1.6 would receive a 1600 mg dose of Totect on Days 1 and 2, and an 800 mg dose of Totect on day 3. Both of these doses fall within the therapeutic range for Tolectin. Despite an overlapping dose, Tolectin would generally be divided to be administered three times a day, whereas Tolectin will be administered once daily for 3 consecutive days. Tolectin and Totect have additional differentiating product characteristics such as indication for use (RA and OA vs. extravasation), strength (200 mg, 400 mg, 600 mg vs. 500 mg), route of administration (oral vs. intravenous), dosage form (tablet/capsule vs. injection), and prescriber population (rheumatologist vs. oncologist).

Tolectin
Totect

Although Tolectin and Totect may overlap in dose, the lack of convincing orthographic similarities and the differentiating product characteristics (indication for use, strength, frequency of administration, route of administration, dosage form and prescriber) minimize the potential for confusion between these two drug products.

2. Cytotec was identified as a name that may sound similar to the proprietary name, Totect. Cytotec is indicated for the prevention of NSAID induced gastric ulcers in patients at high risk of complication from gastric ulcers as well as patients at high risk of developing gastric ulcerations.

   Although Cytotec contains 3 syllables and Totect only contains 2 syllables, the names sound similar because the ending of Cytotec ("-totec") sounds like the proprietary name, Totect. The differentiating phonetic factor is the first syllable of Cytotec ("Cy"-). Although Cytotec and Totect are dosed using different units (mcg vs. mg), they may share an overlapping numerical dose (800 mg vs. 800 mcg) if a patient has a BSA of 1.6. However, Cytotec and Totect differ in indication for use (gastric ulcers vs. extravasation), strength (100 mcg and 200 mcg vs. 500 mg), frequency of administration (four times a day vs. once daily for 3 days), route of administration (oral vs. intravenous), dosage form (injection vs. tablets), and prescriber population (gastroenterologist vs. oncologist). Although Cytotec and Totect share a slight phonetic similarity, the differentiating product characteristics will help to minimize the risk of confusion between the two drugs.

3. Tobrex was identified as a name that may look and sound similar to Totect. Tobrex is indicated for the treatment of external ocular infections caused by susceptible bacteria.

   Tobrex and Totect contain 2 syllables and are 6 letters in length. The similar appearance between Tobrex and Totect stem from the fact that each name begins with the same "To", and end with letters that may look similar when scripted ("-ex" vs. "-ct") (see example below). Also, the third letter of each name contains an upstroke. The verbal similarity stems from the fact that the first syllable of each name is identical ("To" pronounced "toe"). However, the "br" and "x" sound of the second syllables of Tobrex helps to distinguish the name from Totect in speech.

   Tobrex

   Totect

   The differentiating product characteristics between Tobrex and Totect include indication for use (eye infection vs. extravasation), strength (0.3% vs. 500 mg), usual dosage (1-2 drops or ½ inch ribbon vs. 1000 mg/m^2 or 500mg/m^2), route of administration (ophthalmic vs. intravenous), frequency of administration (every 4 hours or BID-TID vs. once daily for 3 days), and prescriber population (ophthalmologist vs. oncologist). Due to the differentiating product characteristics and context of use, DMETS believes the potential for confusion between Tobrex and Totect is minimal.

4. Sutent was identified as a name that may look similar to Totect when scripted. Sutent is indicated for the treatment of GI stromal tumor (GIST) and advanced renal cell carcinoma (RCC).

   Sutent and Totect contain 6 letters and they possess upstrokes in the same position which contributes to the visual similarity of this name pair. Additionally, the beginning letters of each name ("Su-" vs. "To-") may look similar when scripted as do the endings of the names (see example below).

   Totect

   Sutent

Both Sutent and Totect may both be prescribed by oncologists. Although Sutent and Totect overlap in frequency of administration (once daily), the duration of treatment differs (daily for 4 weeks and then 2 weeks off vs. for 3 days). Additional differentiating product characteristics include indication for use (GIST/RCC vs. extravasation), strength (12.5 mg, 25 mg, and 50 mg vs. 500 mg), usual dosage (50 mg vs. 500 mg/m^2 and 1000 mg/m^2), route of administration (oral vs. intravenous), and dosage form (capsules vs. injection).

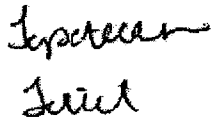
Despite orthographic similarities, the differentiating product characteristics between Sutent and Totect (duration of treatment, strength, dose, route, dosage form and indication for use) will help to minimize the potential for confusion.

5. Topotecan was identified a name that may sound and look similar to Totect. Topotecan is the established name for Hycamtin. It is indicated for the treatment of ovarian cancer, small cell lung cancer, and cervical cancer.

   Topotecan and Totect may look and sound similar as they both begin with "To-", and they both contain the letters "-te-" in the middle of the name. However, Topotecan contains 9 letters and 4 syllables whereas Totect contains only 6 letters and 2 syllables. Additionally, the downstroke of the letter "p" and the length of the name, Topotecan, help to distinguish the names visually. Furthermore, the phonetic pronunciation of the names also distinguishes between them (toe-poe-TEE-can vs. TOE-tect).

   Both drugs share overlapping routes of administration (intravenous), dosage form (injection), frequency of administration and duration of treatment (once daily for 3 days), as well as prescriber population (oncologist). However, Topotecan and Totect differ in indication for use (ovarian, cervical and lung cancer vs. extravasation), strength (4 mg/vial vs. 500 mg/vial), and usual dosage (0.75 mg/m^2 and 1.5 mg/m^2 vs. 500 mg/m^2 and 1000 mg/m^2). It should be noted that the many of medical facilities are taking more precautions when writing and checking chemotherapy orders. For example, facilities may require practitioners to write both the proprietary and established name on chemotherapy orders in addition to the indication for use, patient information (height, weight, BSA), and total dose to be administered. Additionally, the dose for Topotecan and Totect will not overlap based on how each product is dosed (0.75 mg/m^2 and 1.5 mg/m^2 vs. 500 mg/m^2 and 1000 mg/m^2).

   Although Topotecan and Totect share some overlapping product characteristics, the lack of convincing orthographic and phonetic similarities minimize the potential for confusion between these two drug products. Furthermore, the differentiating product characteristics (usual dose and total dose to be administered) further minimize the risk of confusion between Topotecan and Totect.



6. Acutect was identified as having look-alike similarities to Totect when scripted. Acutect is a technetium Tc99m product indicated for the scintigraphic imaging of acute venous thrombosis in the lower extremities.

   The visual similarities stem from the similar appearance of the capital letter "A" to a lowercase "t" when scripted. Additionally, Acutect and Totect may look similar because they share the same last four letters (-tect"). However, the letter "u" in Acutect helps to slightly differentiate and lengthen the name from Totect.

   Both drugs share overlapping route of administration (intravenous) and dosage form (injection). Conversely, Acutect and Totect differ in indication for use (imaging vs. extravasation), usual

dosage (100 mcg bibapcitide radiolabeled with 20 mCi of technetium 99m vs. 500 mg/m^2 and 1000 mg/m^2), frequency of administration (one time vs. once daily for 3 days), prescriber population (nuclear medicine radiologist vs. oncologist), and storage conditions (refrigerator vs. room temperature). Although both drug products may be used in an inpatient setting, they will be prepared in separate locations (nuclear medicine department vs. oncology department). Although Acutect and Totect share orthographic similarities, the differentiating product characteristics will help to minimize the potential for confusion between these two drug products.

Acutect
Totect

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Totect, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENT

We note the sponsor uses "dexrazoxane as hydrochloride" for the established name of this product. We recommend revising the established name to read as "dexrazoxane for injection" because this is a powder for injection and the strength is based on dexrazoxane and not the hydrochloride salt. The hydrochloride salt can be incorporated into the "Each vial contains..." statement as follows: "Each vial contains dexrazoxane hydrochloride equivalent to 500 mg of dexrazoxane". For consistency purposes, revise the established name to read as "Dexrazoxane for Injection" on all labels and labeling.

B. CONTAINER LABELS for the Totect Drug Substance

a. Increase the prominence of the proprietary name as it appears small on the label.

b. The trademark symbol (™) is almost as prominent as the font size used for the proprietary name. Decrease the size of the trademark symbol so it is not confused as part of the proprietary name.

c. Delete the word "Powder" that appears in conjunction with the proprietary name. This is misleading as it appears that the proprietary name is "Totect Powder" rather than "Totect". Additionally, the dosage form of this product is presented with the established name. See General Comment A.

d. The product strength is presented as [redacted] Delete the phrase [redacted] as this is not representative of the strength. The strength should only be "500 mg". b(4)

e. Include the route of administration on the vial. The statement should read as follows: "For Intravenous Use Only following reconstitution and dilution".

f. Include a statement on the label that indicates that each vial is a single use vial and to discard the unused portions.

g. The unit for the storage temperature was omitted from the label as it currently reads: "Store below 25°". Please revise the storage temperature to include the appropriate unit of measure (°C).

h. The following statement may be confusing: [redacted] b(4
Revise this statement to read as follows in order to minimize confusion: "Protect from light. Keep vial in carton until ready for use".

i. Decrease the prominence of the sponsors name (Topotarget) at the bottom of the container label. It appears almost as prominent as the proprietary name and may be misinterpreted as the proprietary name or even as the established name of the product.

C. CONTAINER LABELS for Solvent for Reconstitution

a. Delete the proprietary name "Totect" from the vial label. This may mislead the reader to believe that the vial actually contains the drug Totect, despite the phrase ' [redacted] b(4

b. The vial labeled "Solvent" should indicate the name of the solvent (e.g., Sterile Water for Injection, Normal Saline for Injection, etc.). In order to minimize confusion, the vial should labeled as "XXXX (name of solvent) for reconstitution" (e.g., Sterile Water for Injection), and labeled as Solvent for Totect. Please revise.

c. Include a statement that indicates the solvent is for reconstitution with only the drug product, Totect.

d. Revise the net volume of the vial to read "50 mL" not "500 mL" as it currently appears on the label.

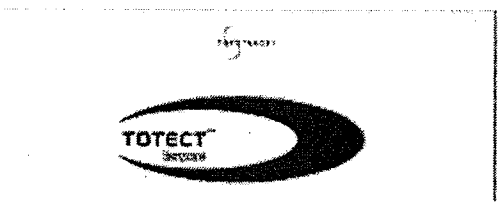
e. Delete the statement ' [redacted] as this may be mistakenly injected into a patient without reconstitution with drug product. b(4)

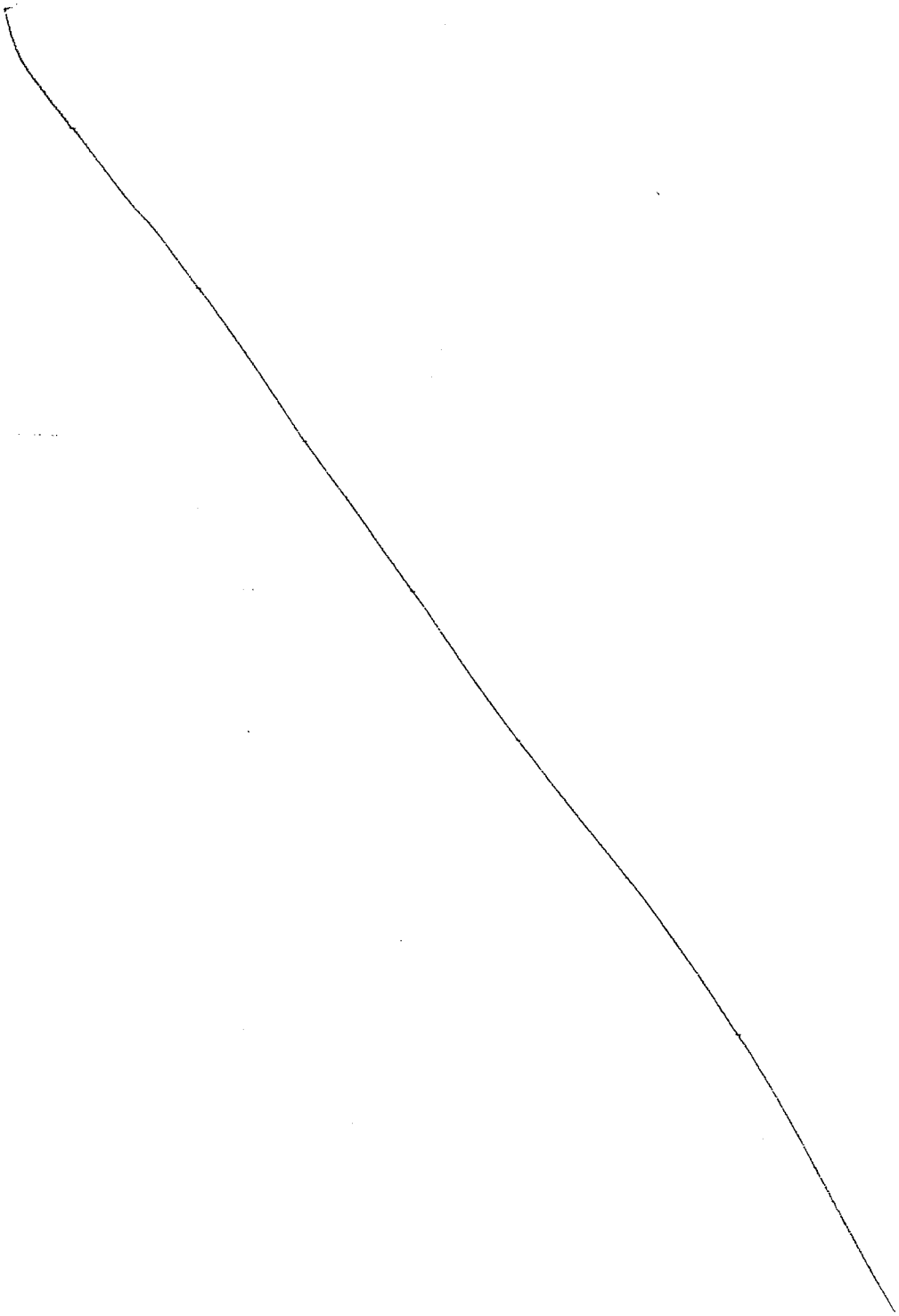
f. Increase the prominence of the statement: "This vial does not contain active drug", by bolding or some other means.

g. See comments B1g, B1h, and B1i.

D. CARTON LABELING

1. The Totect horseshoe-shaped logo is distracting (see below). It also makes the drug name look like a company logo rather than a proprietary name. The logo should not interfere with, or be more prominent than the proprietary name. Thus, the sponsor should decrease the prominence or relocate the logo away from the proprietary name to avoid distracting the reader. Additionally, increase the size of the proprietary name and established name.





b(4)

E. PACKAGE INSERT

1. See General Comment.

2. Dosage and Administration section

   a. Preparation and Administration subsection

      In the preparation and administration subsection, the first sentence states that "the indicated dose should be administered as an intravenous infusion over 1 to 2 hours". However, the last sentence of this section states that the infusion

should be "...given as a rapid drip intravenous infusion...." Please clarify if the latter statement is pertinent only to Day 2 or Day 3 as this statement may be confusing for the user. Additionally, please clarify the term "rapid drip infusion" (e.g., bolus). If this is not intended as a bolus, then the rate of infusion should be clarified.

b. Directions for Mixing and Diluting subsection

i. Revise the title of this subsection the read "Directions for Reconstitution and Dilution" as this may be easier for the reader to understand. The sentence following the title of the subsection should read "Read this entire section carefully before reconstitution and dilution".

ii. The following paragraph may be confusing to the reader:

Before infusion each vial of Totect™ 500 mg powder, must be mixed with 50 ml Totect™ solvent for injection. The mixed solution should be further diluted in 1000 ml 0.9% NaCl (500 ml of 0.9% NaCl on day 3 where half of the dose is given).

Revise this section as follows in order to minimize confusion and to provide clarity:

"Before infusion, each vial of Totect must be reconstituted with 50 mL of solvent for injection. The reconstituted solution should be further diluted in 1000 mL of 0.9%NaCl on Day1 and Day 2, and with 500 mL of 0.9% NaCl on Day 3 where half the dose is given".

c. Preparation of the Totect mixed and diluted solution

i. In order to simplify this section, the sponsor should consider organizing the instructions into two sections as follows. The terminology used should be consistent throughout the labeling, and the directions should provide clear, concise instructions:

Reconstitution of Totect

1. Leave this statement as is (Using a 60 mL syringe...).

2. Revise this statement to include to amount of solvent needed, and instruct the user on how to dissolve the medication (e.g., gently swirl, allow solution to dissolve at room temperature, etc.). For example: Inject 50 mL of (name of solvent) into the Totect vial. Gently swirl the vial until the medication is dissolved.

3. Relocate this statement to step 3 in order to indicate the concentration of Totect once it is reconstituted. Additionally, revise this statement as follows to maintain consistency with terminology and to provide clear, concise instructions. For example: The reconstituted solution contains 10 mg/mL of dexrazoxane HCl.

4. Revise this step as follows: Withdraw the desired of dissolved solution back into the 60 mL syringe.

5. Clarify these steps by breaking them up into separate steps (step 5 and step 6): "The mixed solution should be further diluted into the infusion bag with 1000 mL...."

6. The last step of the reconstitution section should be: "The reconstituted solution should be used immediately after preparation. It contains no antibacterial preservative."

Dilution of Totect

The reconstituted Totect solution should be further diluted in 1000 mL of 0.9% NaCl on Day 1 and Day 2, and in 500 mL of 0.9% NaCl on Day 3. The diluted solution should be used immediately after preparation. It contains not antibacterial preservative.

7. Inject the calculated volume of reconstituted Totect into the infusion bag of 1000 mL of 0.9% NaCl (Day 1 and Day 2) or 500 mL of 0.9%NaCl (Day 3). **The solution must not be mixed with any other drugs.**

8. Modify this statement as follows: "Repeat step 1-7 in order to obtain the required dose".

9. Leave this statement as is (Totect should be aseptically administered as a 1-2 hour infusion under room temperature...).

ii. The last sentence of the last paragraph of this section is unclear. It reads: "The product is stable for 4 hours from the time of mixing and diluting when stored below 25°C (77°F)". What is meant by "when stored below 25°C (77°F)? Does this mean that the reconstituted product must be refrigerated or is it stable at room temperature for 4 hours? Please clarify. Additionally, revise the terms "mixing" and "diluting" to be "reconstitution" and "dilution".

d. Storage section

Include the statement "Protect from light", as it appears on the carton labeling and container labels.

APPEARS THIS WAY ON ORIGINAL

Appendix A

Totect prescription study results

Requisition #1	Requisition #2	Verbal
Testect	Totect	Kotek
Tetect	Toctect	Toltec
Toact	Toctect	Toltec
Totect	Tolect	Tortec
Totect	Totect	Totec
Totect	totect	Totec
Totect	Totect	Totec
Totect	Totect	Totec
Totect	Totect	Totec
totect	Totect	Totec
Totek	Totect	Totec
Totuk	Totect	totec
Tutect	Totect	Toteck
Tutect	Totect	Totek
Tutect	Totect	Totet
	Totect	Tutec

APPEARS THIS WAY ON ORIGINAL

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

/s/

Felicia Duffy
7/18/2006 03:46:26 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/18/2006 03:49:17 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/18/2006 04:37:25 PM
DRUG SAFETY OFFICE REVIEWER