HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Totect safely and effectively. See full prescribing information for Totect.

Totect® (dexrazoxane) for injection, for intravenous use

Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3)	11/2018
Warnings and Precautions (5.1)	02/2018
Warnings and Precautions (5.2)	02/2018
Warnings and Precautions (5.3)	02/2018

----------INDICATIONS AND USAGE----------

- Totect is a cytoprotective agent indicated for the treatment of extravasation resulting from intravenous anthracycline chemotherapy. (1)

---------DOSAGE AND ADMINISTRATION---------

- Reconstitute and further dilute Totect before use. (2.3)
- Administer Totect by intravenous infusion over 1 to 2 hours once daily for 3 consecutive days. (2.1, 2.4)
- Initiate the first infusion as soon as possible and within the first six hours after extravasation. (2.1)

	Recommended dose	Maximum daily dose
Day one:	1000 mg/m²	2000 mg
Day two:	1000 mg/m²	2000 mg
Day three:	500 mg/m²	1000 mg

- Reduce dose by 50% for patients with creatinine clearance < 40 mL/min. (2.2)

-------DOSAGE FORMS AND STRENGTHS -------

- For Injection: 500 mg as a sterile, pyrogen-free lyophilized powder in a single dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

None. (4)

---------WARNINGS AND PRECAUTIONS----------

- Myelosuppression: Dexrazoxane is associated with leukopenia, neutropenia, and thrombocytopenia. Perform hematological monitoring. (5.1)
- Anaphylactic/Hypersensitivity Reactions: Monitor for signs and symptoms. Permanent treatment discontinuation should be considered for severe hypersensitivity reactions. (5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the risk to a fetus and to use effective contraception (5.3, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥15%) are nausea, pyrexia, injection site pain, vomiting, and postoperative infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-877-484-2700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Dimethyl sulfoxide: Totect is not recommended for use with topical dimethyl sulfoxide (DMSO). (7.1)

---------USE IN SPECIFIC POPULATIONS---------

- Lactation: Advise women not to breastfeed. (8.2)
- Renal impairment: Monitor patient for signs of hematological toxicity. Reduce the Totect dose by 50% in patients with creatinine clearance values < 40 mL/min. (8.6)
- Hepatic impairment: Use in patients with hepatic impairment is not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Totect® is indicated for the treatment of extravasation resulting from intravenous anthracycline chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Reconstitute and further dilute Totect before use *[see Dosage and Administration (2.3)]*.

Administer Totect once daily for 3 consecutive days. Initiate the first infusion as soon as possible and within the first six hours after extravasation *[see Dosage and Administration (2.4)]*.

The individual dosage is based on calculation of the Body Surface Area (BSA) up to a maximum dose of 2000 mg (each on Day 1 and 2) and 1000 mg (Day 3), corresponding to a BSA of 2 m^2.

The recommended dose is:	Maximum daily dose:
Day one: 1000 mg/m^2	2000 mg
Day two: 1000 mg/m^2	2000 mg
Day three: 500 mg/m^2	1000 mg

2.2 Dose Modifications
Reduce the Totect dose by 50% in patients with creatinine clearance values < 40 mL/min.

2.3 Directions for Mixing and Final Dilution
Read this entire section carefully before mixing and diluting.
Aseptic technique should be used during preparation.

Use caution when handling and preparing the reconstituted solution. The use of gloves is recommended. If Totect powder or solutions contact the skin or mucosae, wash exposed area immediately and thoroughly with soap and water. Follow special handling and disposal procedures.[1]

Totect should not be mixed or administered with any other drug during the infusion.

The prepared solution of Totect is slightly yellow.

Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Solutions containing a precipitate should be discarded. Vials are for single use only. Unused solution should be discarded.

Totect solution can be prepared with **EITHER** Sterile Water for Injection, USP and Lactated Ringer's Injection **OR** 0.167M sodium lactate injection and 0.9% Sodium Chloride Injection– refer carefully to the instructions below.

Preparation of Totect Solution using Sterile Water for Injection, USP and Lactated Ringer's Injection, USP

Step 1. Reconstitute each Totect vial with 50 mL of Sterile Water for Injection, USP. Once reconstituted, the reconstituted Totect solution contains 10 mg/mL of Totect.

Step 2. Calculate the volume of the 10 mg/mL reconstituted Totect solution needed for the recommended dose. In order to obtain the required dose, more than one vial may be needed. The reconstituted solution should be further diluted within 30 minutes after initial reconstitution. It contains no antibacterial preservative.

Step 3. Withdraw the calculated volume from the reconstituted Totect solution and further dilute into an infusion bag containing 1000 mL of Lactated Ringer's Injection. Do not mix Totect with any other drugs.

Use the Totect infusion bag immediately after preparation. If not used immediately, the product is stable for 4 hours from the time of preparation when stored at room temperature or for up to 12 hours when stored refrigerated between 2-8ºC (36-46°F).

Preparation of Totect Solution using 0.167M Sodium Lactate Injection and 0.9% Sodium Chloride Injection

Step 1. Reconstitute each Totect vial with 50 mL of 0.167M sodium lactate injection solution.

> **Preparation of 0.167M sodium lactate injection solution**
>
> Dilution of sodium lactate injection to 0.167M is required before using it to reconstitute Totect. Add 1.67 mL of 5 mEq/mL sodium lactate injection to 50 mL Sterile Water for Injection, USP to make 50 mL of 0.167M sodium lactate injection solution.

Once reconstituted, the reconstituted Totect solution contains 10 mg/mL of Totect.

Step 2. Calculate the volume of the 10 mg/mL reconstituted Totect solution needed for the recommended dose. In order to obtain the required dose, more than one vial may be needed. The reconstituted solution should be further diluted within 30 minutes after initial reconstitution. It contains no antibacterial preservative.

Step 3. Withdraw the calculated volume from the reconstituted Totect solution and further dilute into an infusion bag containing 1000 mL of 0.9% Sodium Chloride Injection. Do not mix Totect with any other drugs.

Use the Totect infusion bag immediately after preparation. If not used immediately, the product is stable for 4 hours from the time of preparation when stored at room temperature or for up to 12 hours when stored refrigerated between 2-8ºC (36-46°F).

2.4 Administration

Do not administer or mix Totect with any other drug during the infusion.

Remove cooling procedures such as ice packs, if used, from the extravasation area at least 15 minutes before Totect administration in order to allow sufficient blood flow to the area of extravasation.

Administer as an intravenous infusion over 1 to 2 hours at room temperature and normal light conditions in a large caliber vein in an extremity/area other than the one affected by the extravasation.

Treatment on Day 2 and Day 3 should start at the same hour (+/- 3 hours) as on the first day.

Perform local examination for extravasation on a regular basis after treatment and until resolution.

If vesicant compounds other than anthracyclines are being used through the same IV access, (e.g. vincristine, mitomycin, and vinorelbine), consider treatments for these other vesicant compounds. Totect is not effective against the effects of vesicants other than anthracyclines *[see Clinical Studies (14)]*.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 500 mg as a sterile, pyrogen-free lyophilized powder in a single dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with Totect is associated with leukopenia, neutropenia, and thrombocytopenia. Grade 2-4 decreased white blood cells (73%), decreased neutrophils (61%), and decreased platelets (26%) occurred in patients treated with Totect and cytotoxic chemotherapy in clinical trials. Febrile neutropenia occurred in 2.5% of patients *[see Adverse Reactions (6.1)]*.

Monitor complete blood counts during treatment with Totect and cytotoxic chemotherapy. The myelosuppression and cytotoxic potential of Totect and cytotoxic chemotherapy (with a nadir occurring on days 10-12) may be additive to that of the chemotherapy administered alone.

5.2 Anaphylactic/Hypersensitivity Reactions

Hypersensitivity reactions including anaphylactic reaction, angioedema, skin reactions, bronchospasm, respiratory distress, hypotension and loss of

consciousness have occurred in patients treated with dexrazoxane products and anthracyclines *[see Adverse Reactions (6)]*. Previous history of allergy to dexrazoxane products should be carefully considered prior to administration. Consider permanent discontinuation in patients with severe hypersensitivity reactions.

5.3 Embryo-Fetal Toxicity

Totect can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In animal reproduction studies, intravenous administration of dexrazoxane to pregnant rats and rabbits during organogenesis resulted in teratogenicity at maternal doses approximately 0.1 and 0.2 times, respectively, the human dose of 1000 mg/m^2. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Totect. Advise males with female partners of reproductive potential to use effective contraception during treatment with Totect and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

In the clinical studies, Totect was administered to patients also receiving chemotherapeutic agents for cancer, and the adverse reaction profile and laboratory abnormalities presented in Tables 1 and 2 reflect the combination of Totect, underlying disease, and already administered chemotherapy. The adverse reaction data reflect exposure to Totect from two clinical studies 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 reactions occurring with ≥ 5% frequency.

Table 1 Adverse Reactions Occurring at ≥ 5% Frequency

System Organ Class (SOC) and Adverse Reaction	Study 1 and 2 Combined (All causalities) % (N=80)
Total number of patients with at least one event	85
General disorders and administration site conditions	58
Pyrexia	21
Injection site pain/injection site discomfort	16
Fatigue	13

Edema peripheral	10
Injection site phlebitis	6
Gastrointestinal disorders	55
Nausea	43
Vomiting	19
Diarrhea	11
Abdominal pain	6
Constipation	6
Infections and infestations	30
Postoperative infection	16
Nervous system disorders	24
Dizziness	11
Headache	6
Skin and subcutaneous disorders	18
Alopecia	14
Respiratory, thoracic and mediastinal disorders	16
Dyspnea	8
Pneumonia	6
Cough	5
Vascular disorders	15
Blood and lymphatic system disorders	14
Anemia	6
Psychiatric disorders	14
Depression	8
Insomnia	5
Musculoskeletal and connective tissue disorders	13
Metabolism and nutrition disorders	10
Anorexia	5
Cardiac disorders	5

Table 2 summarizes laboratory abnormalities from studies 1 and 2.

Table 2: Laboratory Abnormalities

Laboratory Abnormality	Grade 3	Grade 4	Grade 2 to 4
	%	%	%
Hematologic			
Decreased hemoglobin	3	0	43
Decreased WBC	25	20	73
Decreased neutrophils	22	24	61
Decreased platelets	21	0	26
Hepatic			
Increased bilirubin	2	0	11
Increased AST	1	1	28
Increased ALT	1	5	22
Increased alkaline phosphatase	0	0	4
Increased LDH	0	0	5
Metabolic			
Increased creatinine	2	2	14
Decreased sodium	5	1	6
Increased calcium total	2	2	7

7 DRUG INTERACTIONS

7.1 Dimethyl sulfoxide

Totect is not recommended for use with topical dimethyl sulfoxide (DMSO). Based on anecdotal reports concurrent use of topical DMSO at the site of tissue injury may reduce the benefit of Totect. Additionally, nonclinical studies using a mouse model that simulates extravasation of anthracyclines has shown that concomitant treatment with topical DMSO decreases the efficacy of systemic dexrazoxane.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Totect can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Limited available data with Totect use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental

outcomes. In animal reproduction studies, intravenous administration of dexrazoxane to pregnant rats and rabbits during organogenesis resulted in teratogenicity at maternal doses that were approximately 0.1 and 0.2 times, respectively, the human dose of 1000 mg/m^2 . Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15–20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant females received intravenous doses of up to 8 mg/kg dexrazoxane during the period of organogenesis. A dose of 8 mg/kg (approximately 0.1 times the human dose of 1000 mg/m²) was teratogenic, resulting in imperforate anus, microphthalmia, and anophthalmia. Doses ≥ 2 mg/kg (approximately 0.01 times the human dose of 1000 mg/m²) caused maternal toxicity.

In an embryo-fetal development study in rabbits, pregnant females received intravenous doses of up to 20 mg/kg (approximately 0.2 times the human dose of 1000 mg/m²) were teratogenic, resulting in several skeletal malformations such as short tail, rib and thoracic malformations, and soft tissue variations including subcutaneous, eye and cardiac hemorrhagic areas, as well as agenesis of the gallbladder and of the intermediate lobe of the lung. Doses ≥ 5 mg/kg (approximately 0.1 times the human dose of 1000 mg/m²) caused maternal toxicity.

In a pre and postnatal development study in rats, intravenous administration of 8 mg/kg dexrazoxane to pregnant rats during organogenesis resulted in impairment of fertility in the male and female offspring. A dose of 8 mg/kg in rats is approximately 0.1 times the human dose of 1000 mg/m^2.

8.2 Lactation

Risk Summary

There are no data on the presence of dexrazoxane in human milk, the effects on the breastfed child, or the effect on milk production. Because of the potential for serious adverse reactions, such as myelosuppression, in a breastfed child from Totect, advise women not to breastfeed during treatment and for 2 weeks following the final dose of Totect.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing should be performed prior to initiation of chemotherapy. Therefore, repeat pregnancy testing prior to administration of Totect is not recommended, because treatment of extravasation of anthracycline chemotherapy should not be delayed.

Contraception

Females
Totect can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Totect.

Males
Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the final dose of Totect *[see Nonclinical Toxicology (13.1)]*.

Infertility
Males
Based on findings in animal studies, Totect may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and effectiveness of Totect in pediatric patients have not been established.

8.5 Geriatric Use
In total, 21% of the patients treated with Totect were age 65 years or older and 9% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection, and it may be useful to monitor renal and hepatic function *[see Dosage and Administration (2.2)]*.

8.6 Renal Impairment
Greater exposure to dexrazoxane may occur in patients with compromised renal function. Monitor patients with impaired renal function for signs of hematological

toxicity. The Totect dose should be reduced by 50% in patients with creatinine clearance values < 40 mL/min. *[see Dosage and Administration (2.2)]*

8.7 Hepatic Impairment

Totect has not been studied in patients with hepatic impairment. Since liver dysfunction (increases in transaminases and bilirubin) may occur (especially after doses of above 1000 mg/m^2 dexrazoxane), it is recommended that routine liver function tests be performed before each administration of dexrazoxane in patients with known liver function disorders. Use in patients with hepatic impairment is not recommended.

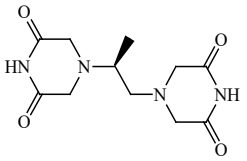
10 OVERDOSAGE

Overdose with dexrazoxane can lead to signs of bone marrow failure. Treatment should be symptomatic. There is no known antidote for dexrazoxane.

11 DESCRIPTION

Totect (dexrazoxane for injection) is a sterile, pyrogen-free lyophilized powder intended for intravenous (IV) administration. Each Totect carton contains 1 single dose vial of Totect (dexrazoxane for injection) 500 mg.

Chemically, dexrazoxane, a cytoprotective agent, is 2,6-piperazinedione,4,4'-(1-methyl-1,2-ethanediyl)bis-,(S)- or (S)-(+)-1,2-bis(3,5-dioxopiperazin-1-yl)propane. The following diagram shows the chemical structure:



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

The finished product is supplied in a sterile form for intravenous infusion only following mixing and diluting.

Each carton contains one 50 mL Type I glass vial. Each vial contains dexrazoxane hydrochloride equivalent to 500 mg dexrazoxane (free base). Hydrochloric Acid, NF is added for pH adjustment. When reconstituted as directed with 50 mL of Sterile Water for injection, USP, each mL contains 10 mg dexrazoxane and the pH of the resultant solution is 1.0 to 3.0. When reconstituted as directed with the

50 mL of 0.167 M sodium lactate injection solution, each mL contains 10 mg dexrazoxane and the pH of the resultant solution is 3.5 to 5.5.

The admixture should be further diluted prior to administration to patients. *[see Dosage and Administration (2.3)]*

Each vial of dexrazoxane for injection is closed with an aluminum flip-off cap covered with a dark red overcap.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which Totect diminishes tissue damage resulting from the extravasation of anthracycline drugs is unknown. Some evidence suggests that dexrazoxane inhibits topoisomerase II reversibly.

12.3 Pharmacokinetics

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

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

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

[a] Coefficient of variation
[b] Steady-state volume of distribution

Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within 2 to 4 hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m²).

In a study of the pharmacokinetics of dexrazoxane following the recommended dosing for patients with anthracycline extravasation, the mean systemic clearance and steady-state volume of distribution of dexrazoxane in six female patients undergoing treatment for anthracycline extravasations at a dose of 1000 mg/m^2 Totect on Days 1 and 2 and 500 mg/m^2 on Day 3 were similar to that observed when administered with doxorubicin. The systemic clearances (mean ± SD) were similar among Day 1 (5.9 ± 2.0 L/h/m^2), Day 2 (6.4 ± 2.1 L/h/m^2), and Day 3 (7.9 ± 3.0 L/h/m^2). The terminal elimination half life did not change over 3 days (2.1-2.2 h). The volume of distribution was 17.9 ~ 22.6 L/m^2.

In vitro studies on dexrazoxane in human microsomes indicated that metabolism is unlikely via cytochrome P450. Qualitative metabolism studies with dexrazoxane have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. The metabolite levels were not measured in the pharmacokinetic studies.

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

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

Effects of Gender
There are no clinically relevant differences in the pharmacokinetics of dexrazoxane between males and females.

Renal insufficiency
The pharmacokinetics of dexrazoxane were assessed following a single 15 minute IV infusion of 150 mg/m² of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean $AUC_{0\text{-inf}}$ value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} < 30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure ($AUC_{0\text{-inf}}$) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} > 80 mL/min) *[see Dosage and Administration (2.2)]*. Monitor patients with renal insufficiency for signs of hematological toxicity *[see Use in Specific Populations (8.6)]*.

Hepatic insufficiency
The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic impairment.

Drug interactions

In vitro studies indicated that dexrazoxane is not an inhibitor for CYP1A, CYP2C9, CYP2C19, CYP2D6 or CYP3A.

In studies of dexrazoxane co-administrated with doxorubicin (50 to 60 mg/m^2) or epirubicin (60 to 100 mg/m^2), there were no indications of significant pharmacokinetic interactions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with dexrazoxane. A study by the National Cancer Institute has reported that long term dosing with razoxane (the racemic mixture of dexrazoxane, ICRF-187, and its enantiomer ICRF-186) is associated with the development of malignancies in rats and possibly in mice.

Dexrazoxane was not mutagenic to bacteria *in vitro* (Ames assay), but was clastogenic in an *in vitro* chromosomal aberrations study in mammalian cells and in an *in vivo* bone marrow micronucleus study in mice.

Fertility studies with dexrazoxane have not be conducted. Testicular atrophy was seen with intravenous dexrazoxane administration at doses as low as 30 mg/kg weekly for 6 weeks in rats (approximately 0.2 times the human dose of 1000 mg/m^2) and as low as 20 mg/kg weekly for 13 weeks in dogs (approximately 0.4 times the human dose of 1000 mg/m^2.

14 CLINICAL STUDIES

Totect was studied in two open-label, single arm, multi-center studies testing whether Totect administration could reduce tissue injury following anthracycline extravasation and thereby reduce or avoid surgical intervention. Totect is not effective against the effects of vesicants other than anthracyclines.

In the studies, eligible patients were receiving single-agent anthracycline intravenously (usually as part of combination chemotherapy) and developed extravasation symptoms of pain, burning, swelling, and/or redness near the infusion site. 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 through a different venous access location. 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 2.0 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.

In total, 80 patients were enrolled and 57 were evaluable. Demographics in the two studies were similar. The median age was 57 years, and sixty-five percent of patients were women. The anthracyclines most commonly associated with extravasation were epirubicin (56%) and doxorubicin (41%). 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 presented with swelling (83%), redness (78%), and pain (43%). The median baseline lesion area was 25 cm^2 (range 1-253 cm^2).

Evaluable patients had to be receiving IV anthracycline (single agent or in combination) at the time of extravasation, to have skin biopsies showing fluorescence, and to 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 non-evaluable patient required surgery for tissue necrosis. Thirteen patients had late sequelae at the event site such as site pain, fibrosis, atrophy, and local sensory disturbance; all were judged as mild except in the one patient who required surgery. None of the 4 patients with CVADs required surgical intervention.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Totect carton contains 1 single dose vial of Totect (dexrazoxane for injection) 500 mg as a sterile, pyrogen-free lyophilized powder.

NDC 66220-110-01: Carton of 1 vial of Totect

Store at 25ºC (77ºF); excursions permitted between 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. Protect from light. Keep vial in carton until ready for use.

Follow special handling and disposal procedures *[see Dosage and Administration (2.3)]*.[1]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Myelosuppression

Inform patients of the possibility of myelosuppression, immunosuppression, and infections. Explain the need for routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever *[see Warnings and Precautions (5.1)]*.

Anaphylactic/Hypersensitivity Reactions

Instruct patients to contact their healthcare provider for signs of an allergic reaction, which could be severe and sometimes fatal *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Totect. Advise females to inform their prescriber of a known or suspected pregnancy. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the final dose of Totect *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment and for 2 weeks following the final dose of Totect *[see Use in Specific Populations (8.2)]*.

PATIENT INFORMATION

Totect® (TOE-TECT)

(dexrazoxane)

injection

What is Totect?

Totect is a prescription medicine used to treat people when anthracycline chemotherapy leaks from your vein into the tissue around the intravenous (IV) site.

It is not known if Totect is safe and effective in children.

Before you receive Totect, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.
- have ever had an allergic reaction to products that contain dexrazoxane.
- are pregnant or plan to become pregnant. Totect can harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with Totect.
  - Females who can become pregnant should use effective birth control during treatment with Totect and for 6 months after the final dose.
  - Males who have female partners who can become pregnant should use effective birth control during treatment with Totect and for 3 months after the final dose.
- are breastfeeding or plan to breastfeed. It is not known if Totect passes into your breast milk. Do not breastfeed during treatment with Totect and for 2 weeks after the final dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal or dietary supplements.

Especially tell your healthcare provider if you use a medicine on the skin (topical) called dimethyl sulfoxide (DMSO). Using a topical DMSO during treatment with Totect may affect how well Totect works.

How will I receive Totect?

- Totect is given to you by your healthcare provider.
- Totect is injected into your vein (intravenous or IV infusion) over 1 to 2 hours each day for three days.

What are the possible side effects of Totect?

Totect can cause serious side effects, including:

- **Low blood cell counts.** Low blood cell counts, including a decrease in white blood cell counts (leukopenia and neutropenia) and a decrease in the blood cells which help your blood to clot (thrombocytopenia), have happened with Totect. Your healthcare provider will do blood tests to check your blood cell counts during treatment with Totect and certain other chemotherapy medicines. You should check your temperature often during treatment with Totect and tell your healthcare provider if you have a fever.
  - **Serious allergic reactions.** Totect can cause allergic reactions that can be severe and may lead to death. Get medical help right away if you get any of the following symptoms of an allergic reaction:
    - trouble breathing
    - swelling of your face, lips, tongue or throat
    - raised bumps (hives)
    - dizziness or lightheadedness
    - faint or pass out

The most common side effects of Totect include:

- nausea
- fever
- blood vessel problems
- pain at the intravenous (IV) site
- vomiting
- infection after surgery

Totect may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of Totect. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Totect.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Totect that is written for health professionals.

What are the ingredients in Totect?
Active ingredient: dexrazoxane (as a hydrochloride salt).
Inactive ingredients: none

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CUMBERLAND® PHARMACEUTICALS ONCOLOGY

CLINIGEN Group plc

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For more information, call 1-877-484-2700.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2018