

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

Indications and Usage (1)	11/2020
Dosage and Administration (2.1 - 2.5)	11/2020
Warnings and Precautions (5.1 - 5.4)	11/2020

INDICATIONS AND USAGE

Totect is a cytoprotective agent indicated for:

- Treatment of extravasation resulting from intravenous anthracycline chemotherapy. (1)
- Reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who will continue to receive doxorubicin therapy to maintain tumor control. Do not use Totect with doxorubicin initiation (1, 5.2)

DOSAGE AND ADMINISTRATION

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

	<u>Recommended dose</u>	<u>Maximum daily dose</u>
--	-------------------------	---------------------------

Day one:	1000 mg/m ²	2000 mg
Day two:	1000 mg/m ²	2000 mg
Day three:	500 mg/m ²	1000 mg

- **Cardiomyopathy:** administer Totect by intravenous infusion over 15 minutes until discontinuation of doxorubicin. (2.2)
- Do **not** administer via intravenous push. (2.5)
- The recommended dosage ratio of Totect to doxorubicin is 10:1, (e.g. 500 mg/m² Totect to 50 mg/m² doxorubicin) (2.2)
- Do not administer doxorubicin before Totect. (2.5)
- Administer doxorubicin within 30 minutes after the completion of Totect infusion. (2.5)
- **Dose Modifications:** reduce dose by 50% for patients with creatinine clearance < 40 mL/min. (2.3, 8.6)

DOSAGE FORMS AND STRENGTHS

- For Injection: 500 mg 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. Dexrazoxane may increase the myelosuppressive effects of chemotherapeutic agents. Perform hematological monitoring. (5.1)
- Concomitant chemotherapy: TOTECT may interfere with the antitumor activity of the chemotherapy regimen. Only use TOTECT in patients who have received a cumulative doxorubicin dose of 300 mg/m² and are continuing doxorubicin therapy. (5.2)
- Cardiac toxicity: TOTECT does not completely eliminate the risk of anthracycline-induced cardiac toxicity. For cardiomyopathy, monitor cardiac function before and periodically during therapy to assess left ventricular ejection fraction (LVEF). If deterioration in cardiac function occurs, consider the benefit of continued therapy against the risk of producing irreversible cardiac damage. (5.3)
- Secondary malignancies: combination of dexrazoxane with chemotherapy may lead to increased risk of secondary malignancies. (5.4)
- Anaphylactic/Hypersensitivity Reactions: monitor for signs and symptoms. Consider permanent discontinuation for severe hypersensitivity reactions. (5.5)
- Embryo-Fetal Toxicity: can cause fetal harm. Advise patients of reproductive potential of the risk to a fetus and to use effective contraception (5.6, 8.1, 8.3)

ADVERSE REACTIONS

Extravasation: The most common adverse reactions (≥15%) are nausea, pyrexia, injection site pain, vomiting, and postoperative infection. (6.1)
Cardiomyopathy: The most common adverse reactions (≥10% and increased versus placebo) was injection site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Clinigen, Inc. at 1-877-776-5385 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Dimethyl sulfoxide: not recommended for use with topical dimethyl sulfoxide (DMSO) in extravasation patients. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: advise women not to breastfeed. (8.2)
- Hepatic impairment: use in extravasation patients with hepatic impairment is not recommended. In cardiomyopathy patients maintain the 10:1 dose proportionality to doxorubicin. (8.7)

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

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose for Extravasation
- 2.2 Recommended Dose for Cardiomyopathy
- 2.3 Dose Modifications
- 2.4 Preparation
- 2.5 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Myelosuppression
- 5.2 Concomitant Chemotherapy
- 5.3 Cardiac Toxicity
- 5.4 Secondary Malignancies
- 5.5 Anaphylactic/Hypersensitivity Reactions
- 5.6 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Dimethyl sulfoxide

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- 8.2 Lactation

- 8.3 Females and Males of Reproductive Potential

- 8.4 Pediatric Use

- 8.5 Geriatric Use

- 8.6 Renal Impairment

- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Extravasation

- 14.2 Cardiomyopathy

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Extravasation

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

Cardiomyopathy

Totect is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who will continue to receive doxorubicin therapy to maintain tumor control. Do not use with the initiation of doxorubicin therapy [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for Extravasation

Reconstitute and further dilute Totect before use [see *Dosage and Administration (2.4)*].

For extravasation, administer Totect via intravenous infusion over 1 to 2 hours 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 (2.5)*].

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 m².

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 Recommended Dose for Cardiomyopathy

Reconstitute and further dilute Totect before use [see *Dosage and Administration (2.4)*].

For cardiomyopathy, administer Totect via intravenous infusion over 15 minutes prior to doxorubicin administration until discontinuation of doxorubicin. Do not administer via an intravenous push [see *Dosage and Administration (2.5)*].

The recommended dosage ratio of Totect to doxorubicin is 10:1 (e.g., 500 mg/m² Totect to 50 mg/m² doxorubicin). Administer doxorubicin within 30 minutes after the completion of Totect infusion.

2.3 Dose Modifications

Dosing in Patients with Renal Impairment

Reduce the Totect dose by 50% in patients with creatinine clearance values < 40 mL/min [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Dosing in Patients with Hepatic Impairment

In patients with anthracycline extravasation, treatment with Totect is not recommended. In patients receiving dexrazoxane for cardiomyopathy, reduce the Totect dosage proportionately (maintaining the 10:1 ratio) in patients with hepatic impairment, since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia [see *Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

2.4 Preparation

Read this entire section carefully before mixing and diluting.

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.

Preparation for the Treatment of Extravasation

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 °C to 8°C (36°F to 46°F).

Preparation for Reducing the Incidence and Severity of Cardiomyopathy

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 to a concentration of 1.3 to 3 mg/mL in Lactated Ringer's Injection. Do not mix Totect with any other drugs.

Use the Totect infusion solution 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 °C to 8°C (36°F to 46°F).

The infusion solutions have a pH of 3.5 to 5.5.

2.5 Administration

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

Administration for Treatment of Extravasation

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 the final diluted solution of Totect 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 intravenous 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 (14.1)*].

Administration for Reducing the Incidence and Severity of Cardiomyopathy

Administer the final diluted solution of Totect by intravenous infusion over 15 minutes before the administration of doxorubicin.

Do **not** administer via an intravenous push.

Administer doxorubicin within 30 minutes after the completion of Totect infusion.

Do **not** use Totect with non-anthracycline chemotherapy regimens.

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. Totect may add to the myelosuppression caused by chemotherapeutic agents.

With extravasation, 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)*].

When used to reduce the incidence and severity of cardiomyopathy, obtain a complete blood count prior to each course of therapy, and administer Totect and chemotherapy only when adequate hematologic parameters are met.

5.2 Concomitant Chemotherapy

Only use TOTECT in those patients who have received a cumulative doxorubicin dose of 300 mg/m² and are continuing with doxorubicin therapy. Do not use with chemotherapy initiation as TOTECT may interfere with the antitumor activity of the chemotherapy regimen.

In a trial conducted in patients with metastatic breast cancer who were treated with fluorouracil, doxorubicin, and cyclophosphamide (FAC) with or without dexrazoxane starting with their first cycle of FAC therapy, patients who were randomized to receive dexrazoxane had a lower response rate (48% vs. 63%) and shorter time to progression than patients who were randomized to receive placebo.

5.3 Cardiac Toxicity

Treatment with TOTECT does not completely eliminate the risk of anthracycline-induced cardiac toxicity. Monitor cardiac function before and periodically during therapy to assess left ventricular ejection fraction (LVEF). If deterioration in cardiac function occurs, consider the benefit of continued therapy against the risk of producing irreversible cardiac damage.

5.4 Secondary Malignancies

Secondary malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) have been reported in studies of pediatric patients who have received dexrazoxane in combination with chemotherapy. The safety and efficacy of TOTECT has not been established for use in pediatric patients. Some adult patients who received dexrazoxane in combination with anti-cancer agents known to be carcinogenic have also developed secondary malignancies, including AML and MDS.

Razoxane is the racemic mixture, of which dexrazoxane is the S(+)-enantiomer. Secondary malignancies (primarily AML) have been reported in patients treated chronically with oral razoxane. In these patients, the total cumulative dose of razoxane ranged from 26 to 480 grams and the duration of treatment was from 42 to 319 weeks. One case of T-cell lymphoma, one case of B-cell lymphoma, and six to eight cases of cutaneous basal cell or squamous cell carcinoma have also been reported in patients treated with razoxane. Long-term administration of razoxane to rodents was associated with the development of malignancies [see *Nonclinical Toxicology (13.1)*].

5.5 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 (6.1)*]. Previous history of allergy to dexrazoxane products should be carefully considered prior to administration. Consider permanent discontinuation in patients with severe hypersensitivity reactions.

5.6 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/m². 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.

Extravasation

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 $\geq 5\%$ frequency.

Table 1 Adverse Reactions Occurring at $\geq 5\%$ 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

Cardiomyopathy

The adverse reaction profile described in this section was identified from randomized, placebo-controlled, double-blind studies in patients with metastatic breast cancer who received the combination of the fluorouracil,

doxorubicin, and cyclophosphamide (FAC) chemotherapy regimen with or without dexrazoxane. The dose of doxorubicin was 50 mg/m² in each of these trials. Treatment was administered every three weeks until disease progression or cardiac toxicity.

Patients in clinical trials who received FAC with dexrazoxane experienced more severe leukopenia, granulocytopenia, and thrombocytopenia than patients receiving FAC without dexrazoxane [see *Warnings and Precautions (5.1)*].

Table 3 below lists the incidence of adverse reactions for patients receiving FAC with either dexrazoxane or placebo in the breast cancer studies. Adverse experiences occurring during courses 1 through 6 are displayed for patients receiving dexrazoxane or placebo with FAC beginning with their first course of therapy (columns 1 and 3, respectively). Adverse experiences occurring at course 7 and beyond for patients who received placebo with FAC during the first six courses and who then received either dexrazoxane or placebo with FAC are also displayed (columns 2 and 4, respectively).

The adverse reactions listed below in Table 3 demonstrate that the frequency of adverse reaction "Pain on Injection" has been greater for dexrazoxane arm, as compared to placebo.

Table 3: Adverse Reactions for Patients Receiving FAC with either Dexrazoxane or Placebo

Adverse Reaction	Percentage (%) of Breast Cancer Patients With Adverse Reaction			
	FAC + Dexrazoxane		FAC + Placebo	
	Courses 1 -6 N = 413	Courses ≥ 7 N = 102	Courses 1-6 N = 458	Courses ≥ 7 N = 99
Alopecia	94	100	97	98
Nausea	77	51	84	60
Vomiting	59	42	72	49
Fatigue/Malaise	61	48	58	55
Anorexia	42	27	47	38
Stomatitis	34	26	41	28
Fever	34	22	29	18
Infection	23	19	18	21
Diarrhea	21	14	24	7
Pain on injection	12	13	3	0
Sepsis	17	12	14	9
Neurotoxicity	17	10	13	5
Streaking/Erythema	5	4	4	2
Phlebitis	6	3	3	5
Esophagitis	6	3	7	4
Dysphagia	8	0	10	5
Hemorrhage	2	3	2	1
Extravasation	1	3	1	2
Urticaria	2	2	2	0
Recall Skin Reaction	1	1	2	0

7 DRUG INTERACTIONS

7.1 Dimethyl sulfoxide

When used to treat extravasation, 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 in this indication. 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/m². 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 \geq 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 \geq 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/m².

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

Totect can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

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

Contraception

Females

Totect can cause fetal harm when administered to a pregnant woman [*see Warnings and Precautions (5.6), 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

Clinical studies of TOTECT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. 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 (2.3)*].

Treatment of Extravasation

In total, 21% of the patients treated with Totect were age 65 years or older and 9% were 75 and older.

Reducing the Incidence and Severity of Cardiomyopathy

In total, 23% of patients that were treated with the recommended dose ratio of dexrazoxane were older than 65 years.

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. Reduce the dose of Totect by 50% in patients with creatinine clearance values < 40 mL/min. [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]

8.7 Hepatic Impairment

Extravasation

Use of Totect for treatment of anthracycline extravasation 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/m² 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.

Cardiomyopathy

In patients receiving dexrazoxane to reduce the incidence and severity of cardiomyopathy, reduce the Totect dosage proportionately (maintaining the 10:1 ratio) in patients with hepatic impairment, since a doxorubicin dose reduction is recommended in the present of hyperbilirubinemia. [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]

10 OVERDOSAGE

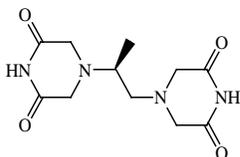
Disposition studies with dexrazoxane have not been conducted in cancer patients undergoing dialysis, but retention of a significant dose fraction (>0.4) of the unchanged drug in the plasma pool, minimal tissue partitioning or binding, and availability of greater than 90% of the systemic drug levels in the unbound form suggest that it could be removed using conventional peritoneal or hemodialysis.

Overdose with dexrazoxane can lead to signs of bone marrow failure. There is no known antidote for dexrazoxane. Instances of suspected overdose should be managed with supportive care until resolution of myelosuppression and related conditions is complete. Management of overdose should include treatment of infections, fluid regulation, and maintenance of nutritional requirements.

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 568 mg dexrazoxane hydrochloride, equivalent to 500 mg dexrazoxane. 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.

The admixture should be further diluted prior to administration to patients. [see *Dosage and Administration (2.1)*]

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 dexrazoxane reduces tissue damage caused by anthracycline-related cardiomyopathy or following anthracycline extravasation is not fully understood. Dexrazoxane is a cyclic derivative of EDTA that penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring-opened chelating agent that interferes with iron-mediated free radical generation. 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.

Table 4: 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/m² Totect on Days 1 and 2 and 500 mg/m² 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/m²), Day 2 (6.4 ± 2.1 L/h/m²), and Day 3 (7.9 ± 3.0 L/h/m²). 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/m².

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-inf} value was twofold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} < 30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} > 80 mL/min) [see *Dosage and Administration* (2.3)]. 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-administered with doxorubicin (50 to 60 mg/m²) or epirubicin (60 to 100 mg/m²), 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 [*see Warnings and Precautions (5.4)*].

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 been 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/m²) and as low as 20 mg/kg weekly for 13 weeks in dogs (approximately 0.4 times the human dose of 1000 mg/m²).

14 CLINICAL STUDIES

14.1 Extravasation

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/m² and the third dose was 500 mg/m². No dose modifications were planned except for patients whose body surface area exceeded 2.0 m², 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 cm² (range 1-253 cm²).

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.

14.2 Cardiomyopathy

The ability of dexrazoxane to reduce the incidence and severity of doxorubicin-induced cardiomyopathy was evaluated in three prospectively randomized placebo-controlled studies. In these studies, patients were treated with a doxorubicin-containing regimen and either dexrazoxane or placebo starting with the first course of chemotherapy. There was no restriction on the cumulative dose of doxorubicin. Cardiac function was assessed by measurement of the left ventricular ejection fraction (LVEF), utilizing resting multigated nuclear medicine (MUGA) scans, and by clinical evaluations. Patients receiving dexrazoxane had significantly smaller mean decreases from baseline in LVEF and lower incidences of congestive heart failure than the control group; however, in the largest study, patients with advanced breast cancer receiving FAC with dexrazoxane had a lower response rate (48% vs. 63%) and a shorter time to progression than patients who received FAC versus placebo.

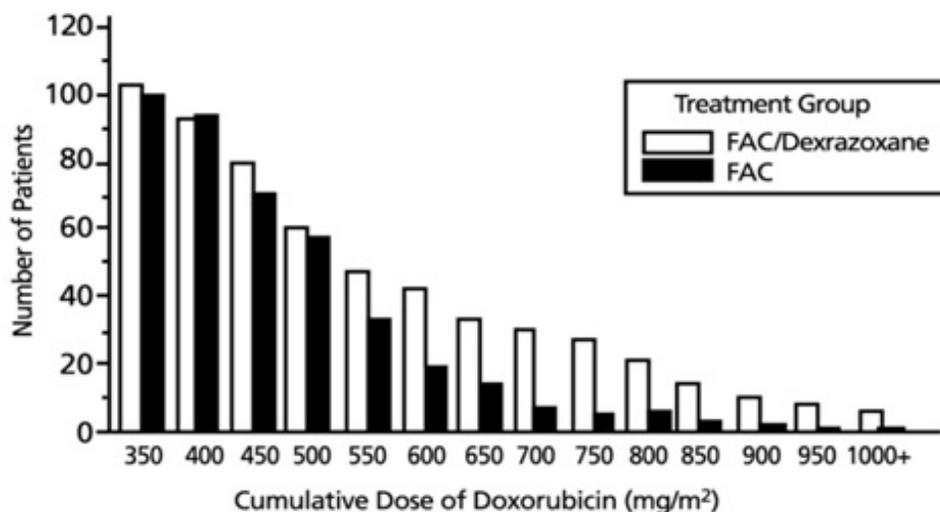
In the clinical trials, patients who were initially randomized to receive placebo were allowed to receive dexrazoxane after a cumulative dose of doxorubicin above 300 mg/m². Retrospective historical analyses showed that the risk of experiencing a cardiac event (see Table 5 for definition) at a cumulative dose of doxorubicin above 300 mg/m² was greater in the patients who did not receive dexrazoxane beginning with their seventh course of FAC than in the patients who did receive dexrazoxane (HR=13.08; 95% CI: 3.72, 46.03; p<0.001). Overall, 3% of patients treated with dexrazoxane developed CHF compared with 22% of patients not receiving dexrazoxane.

Table 5: Definition of Cardiac Events

1. Development of congestive heart failure, defined as having two or more of the following:
 - a. Cardiomegaly by X-ray
 - b. Basilar Rales
 - c. S3 Gallop
 - d. Paroxysmal nocturnal dyspnea and/or orthopnea and/or significant dyspnea on exertion.
2. Decline from baseline in LVEF by $\geq 10\%$ and to below the lower limit of normal for the institution.
3. Decline in LVEF by $\geq 20\%$ from baseline value.
4. Decline in LVEF to $\geq 5\%$ below lower limit of normal for the institution.

Figure 1 shows the number of patients still on treatment at increasing cumulative doses.

Figure 1 Cumulative Number of Patients On Treatment FAC vs. FAC/Dexrazoxane Patients Receiving at Least Seven Courses of Treatment



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 76310-110-01: Carton of 1 vial of Totect

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [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 (2.4)*].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 (5.5)*].

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 (5.6) 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)*].

Manufactured for: Clinigen, Inc. Yardley, PA 19067

CLINIGEN

Totect® is a registered trademark owned by the Clinigen Group.
For additional information, contact Clinigen, Inc. 1-877-776-5385.

US Patent No 6,727,253 B2

PATIENT INFORMATION

Totect® (TOE-TECT)
(dexrazoxane)
injection

What is Totect?

Totect is a prescription medicine used:

- to treat anthracycline chemotherapy leaks from your vein into the tissue around the intravenous (IV) site.
- in women with breast cancer that has spread to other parts of the body (metastatic) and are receiving a medicine called doxorubicin. Totect is used to reduce the occurrence and severity of heart muscle problems that may happen with doxorubicin treatment.

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 heart 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 or think you may be 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:

- are receiving other chemotherapy treatments.
- 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 into your vein (intravenous or IV infusion).
 - To treat anthracycline chemotherapy leaks, you will receive Totect over 1 to 2 hours each day for three days.
 - To reduce the occurrence and severity of heart muscle problems, you will receive Totect over 15 minutes before your doxorubicin treatment.

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. If you are receiving Totect to reduce the occurrence and severity of heart muscle problems, your healthcare provider will do blood tests to check your blood cell counts before each treatment with Totect and chemotherapy. You should check your temperature often during treatment with Totect and tell your healthcare provider right away if you have a fever.
- **Heart problems.** Treatment with Totect does not completely remove your risk of heart problems caused by anthracycline chemotherapy. Your healthcare provider will monitor your heart function before and during treatment with Totect.
- **Secondary cancers.** New cancers have happened in some people treated with Totect in combination with certain anti-cancer treatments. This includes certain blood cancers, such as acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).
- **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
 - dizziness or lightheadedness

- swelling of your face, lips, tongue or throat
- faint or pass out
- raised bumps (hives)

The most common side effects of Totect in people treated for anthracycline chemotherapy leaks include:

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

The most common side effect of Totect in women with metastatic breast cancer to reduce the occurrence and severity of heart muscle problems is pain at the intravenous (IV) site.

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. 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

Manufactured for: Clinigen, Inc. Yardley, PA 19067

CLINIGEN

Totect® is a registered trademark owned by the Clinigen Group.
For additional information, contact Clinigen, Inc. 1-877-776-5385.
US Patent No 6,727,253 B2