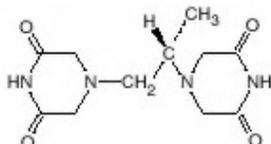


**DEXRAZOXANE HYDROCHLORIDE- dexrazoxane**  
**Mylan Institutional LLC**

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**DESCRIPTION**

Dexrazoxane for injection is a sterile, pyrogen-free lyophilizate intended for intravenous administration. It is a cardioprotective agent for use in conjunction with doxorubicin.

Chemically, dexrazoxane is (S)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione. The structural formula is as follows:



Dexrazoxane, a potent intracellular chelating agent is a derivative of EDTA. Dexrazoxane is a whitish crystalline powder that melts at 191° to 197°C. It is sparingly soluble in water and 0.1 N HCl, slightly soluble in ethanol and methanol and practically insoluble in nonpolar organic solvents. The pK<sub>a</sub> is 2.1. Dexrazoxane has an octanol/water partition coefficient of 0.025 and degrades rapidly above a pH of 7.0.

Dexrazoxane for injection is available in 250 mg and 500 mg single use only vials.

Each 250 mg vial contains dexrazoxane hydrochloride equivalent to 250 mg dexrazoxane. Hydrochloric Acid, NF is added for pH adjustment. When reconstituted as directed with the 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP diluent provided, each mL contains: 10 mg dexrazoxane. The pH of the resultant solution is 3.5 to 5.5.

Each 500 mg vial contains dexrazoxane hydrochloride equivalent to 500 mg dexrazoxane. Hydrochloric Acid, NF is added for pH adjustment. When reconstituted as directed with the 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP diluent provided, each mL contains: 10 mg dexrazoxane. The pH of the resultant solution is 3.5 to 5.5.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

The mechanism by which dexrazoxane for injection exerts its cardioprotective activity is not fully understood. Dexrazoxane is a cyclic derivative of EDTA that readily 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 thought to be responsible, in part, for anthracycline induced cardiomyopathy.

**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/m<sup>2</sup> with 60 mg/m<sup>2</sup> of doxorubicin, and at a fixed dose of 500 mg/m<sup>2</sup> with 50 mg/m<sup>2</sup> 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/m<sup>2</sup>. The mean peak plasma concentration of dexrazoxane was 36.5 mcg/mL at the end of the 15 minute infusion of a 500 mg/m<sup>2</sup> dose of dexrazoxane for injection administered 15 to 30 minutes prior to the 50 mg/m<sup>2</sup> doxorubicin dose. The important

pharmacokinetic parameters of dexrazoxane are summarized in Table 1:

**Table 1: Summary of Mean (% CV\*) Dexrazoxane Pharmacokinetic Parameters at a Dosage Ratio of 10:1 of Dexrazoxane for Injection:Doxorubicin**

Dose Doxorubicin (mg/m <sup>2</sup> )	Dose Dexrazoxane for Injection (mg/m <sup>2</sup> )	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m <sup>2</sup> )	Renal Clearance (L/h/m <sup>2</sup> )	†Volume of Distribution (L/m <sup>2</sup> )
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 (55)

\* Coefficient of variation

† 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/m<sup>2</sup>). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m<sup>2</sup> dexrazoxane along with 50 mg/m<sup>2</sup> doxorubicin were 15.15 L/h/m<sup>2</sup> and 36.27 L/m<sup>2</sup>, respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. Qualitative metabolism studies with dexrazoxane for injection 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/m<sup>2</sup> dose of dexrazoxane for injection was excreted in the urine.

### Protein Binding

*In vitro* studies have shown that dexrazoxane for injection is not bound to plasma proteins.

### Special Populations

#### Pediatric

The pharmacokinetics of dexrazoxane for injection have not been evaluated in pediatric patients.

#### Gender

Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 mL/min/m<sup>2</sup> versus 133 mL/min/m<sup>2</sup>). This gender effect is not clinically relevant.

#### Renal Insufficiency

The pharmacokinetics of dexrazoxane for injection were assessed following a single 15 minute IV infusion of 150 mg/m<sup>2</sup> of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL<sub>CR</sub>) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC<sub>0-inf</sub> value was 2-fold greater in subjects with moderate (CL<sub>CR</sub> 30 to 50 mL/min) to severe (CL<sub>CR</sub> < 30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure (AUC<sub>0-inf</sub>) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL<sub>CR</sub> >80 mL/min) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

#### Hepatic Insufficiency

The pharmacokinetics of dexrazoxane for injection have not been evaluated in patients with hepatic impairment. The dexrazoxane for injection dose is dependent upon the dose of doxorubicin (see DOSAGE AND ADMINISTRATION). Since a doxorubicin dose reduction is recommended in the

presence of hyperbilirubinemia, the dexrazoxane for injection dosage is proportionately reduced in patients with hepatic impairment.

## Drug Interactions

There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m<sup>2</sup>) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m<sup>2</sup>) in a crossover study in cancer patients.

## Clinical Studies

The ability of dexrazoxane for injection to prevent/reduce the incidence and severity of doxorubicin-induced cardiomyopathy was demonstrated in three prospectively randomized placebo-controlled studies. In these studies, patients were treated with a doxorubicin-containing regimen and either dexrazoxane for injection 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 for injection had significantly smaller mean decreases from baseline in LVEF and lower incidences of congestive heart failure than the control group. The difference in decline from baseline in LVEF was evident beginning with a cumulative doxorubicin dose of 150 mg/m<sup>2</sup> and reached statistical significance in patients who received  $\geq 400$  mg/m<sup>2</sup> of doxorubicin. In addition to evaluating the effect of dexrazoxane for injection on cardiac function, the studies also assessed the effect of the addition of dexrazoxane for injection on the antitumor efficacy of the chemotherapy regimens. In one study (the largest of three breast cancer studies), patients with advanced breast cancer receiving fluorouracil, doxorubicin and cyclophosphamide (FAC) with dexrazoxane for injection had a lower response rate (48% vs. 63%;  $p = 0.007$ ) and a shorter time to progression than patients who received FAC vs. placebo, although the survival of patients who did or did not receive dexrazoxane for injection with FAC was similar.

Two of the randomized breast cancer studies evaluating the efficacy and safety of FAC with either dexrazoxane for injection or placebo were amended to allow patients on the placebo arm who had attained a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup> (six courses of FAC) to receive FAC with open-label dexrazoxane for injection for each subsequent course. This change in design allowed examination of whether there was a cardioprotective effect of dexrazoxane for injection even when it was started after substantial exposure to doxorubicin.

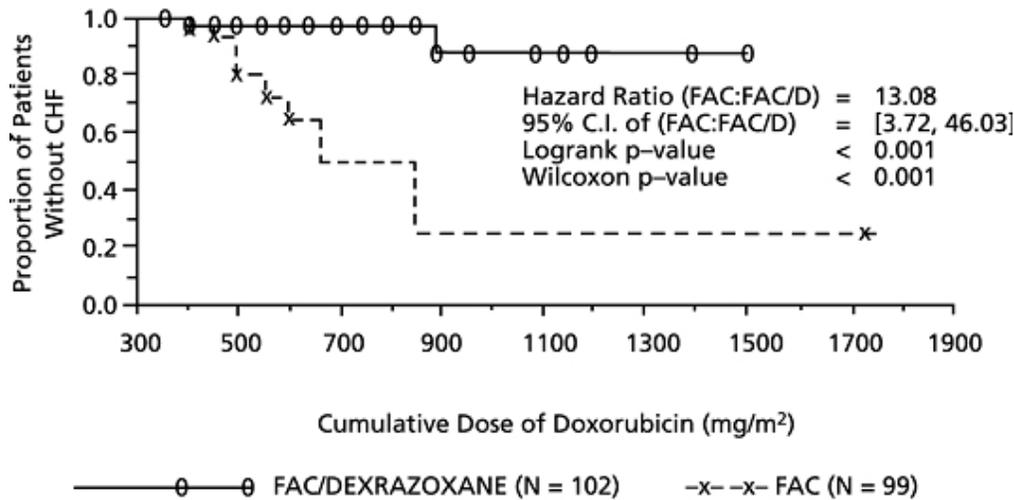
Retrospective historical analyses were then performed to compare the likelihood of heart failure in patients to whom dexrazoxane for injection was added to the FAC regimen after they had received six (6) courses of FAC (and who then continued treatment with FAC therapy) with the heart failure rate in patients who had received six (6) courses of FAC and continued to receive this regimen without added dexrazoxane for injection. These analyses showed that the risk of experiencing a cardiac event (see Table 2 for definition) at a given cumulative dose of doxorubicin above 300 mg/m<sup>2</sup> was substantially greater in the 99 patients who did *not* receive dexrazoxane for injection beginning with their seventh course of FAC than in the 102 patients who did receive dexrazoxane for injection (see Figure 1).

### Table 2: The Development of Cardiac Events is Shown by:

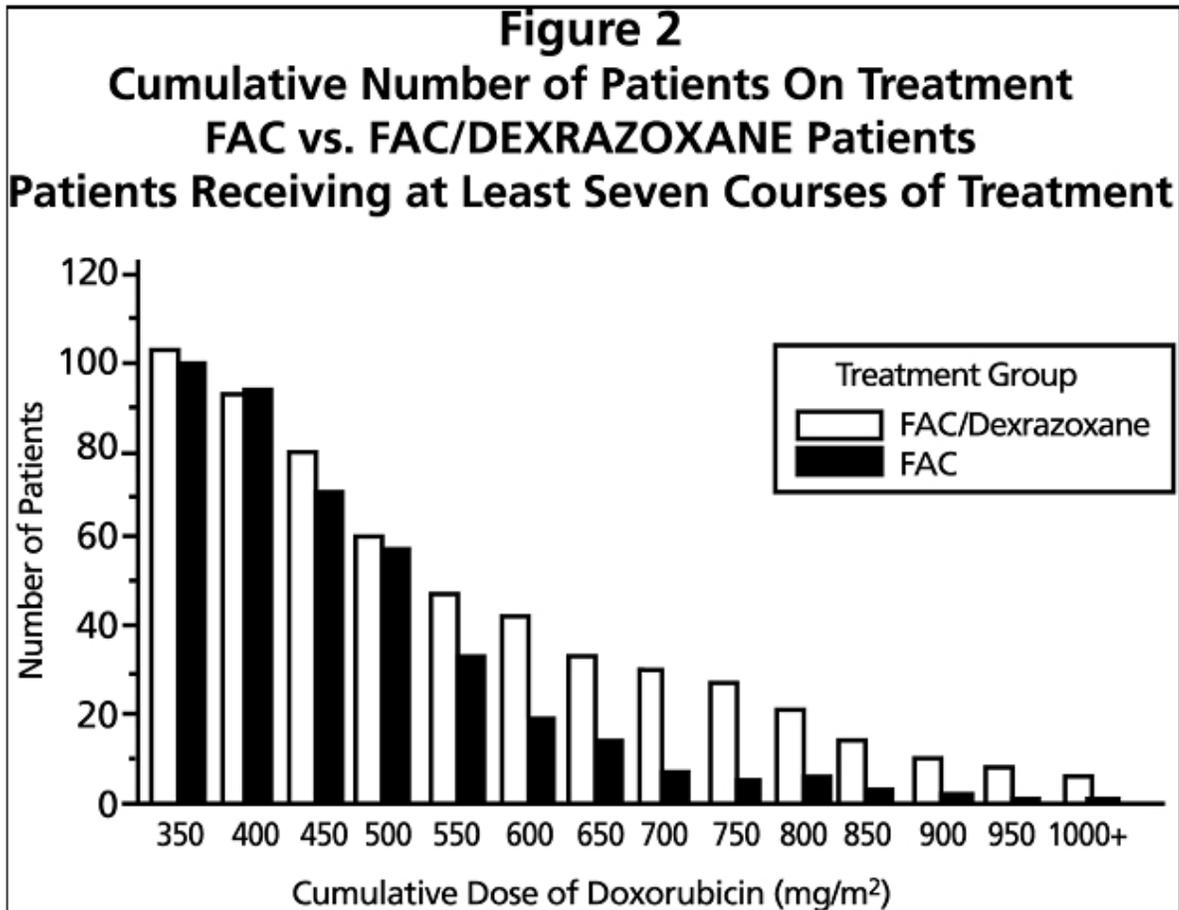
1. Development of congestive heart failure, defined as having two or more of the following:
  - Cardiomegaly by X-ray
  - Basilar Rales
  - S3 Gallop
  - Paroxysmal nocturnal dyspnea and/or orthopnea and/or significant dyspnea on exertion.
2. Decline from baseline in LVEF by  $\geq 10\%$  and to below 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 displays the risk of developing congestive heart failure by cumulative dose of doxorubicin in patients who received dexrazoxane for injection starting with their seventh course of FAC compared to patients who did not. Patients unprotected by dexrazoxane for injection had a 13 times greater risk of developing congestive heart failure. Overall, 3% of patients treated with dexrazoxane for injection developed CHF compared with 22% of patients not receiving dexrazoxane for injection.

**Figure 1**  
**Doxorubicin Dose at Congestive Heart Failure (CHF)**  
**FAC vs. FAC/DEXRAZOXANE Patients**  
**Patients Receiving At Least Seven Courses of Treatment**



Because of its cardioprotective effect, dexrazoxane for injection permitted a greater percentage of patients to be treated with extended doxorubicin therapy. Figure 2 shows the number of patients still on treatment at increasing cumulative doses.



In addition to evaluating the cardioprotective efficacy of dexrazoxane for injection in this setting, the time to tumor progression and survival of these two groups of patients were also compared. There was

a similar time to progression in the two groups and survival was at least as long for the group of patients that received dexrazoxane for injection starting with their seventh course, i.e., starting after a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup>. These time to progression and survival data should be interpreted with caution, however, because they are based on comparisons of groups entered sequentially in the studies and are not comparisons of prospectively randomized patients.

## **INDICATIONS AND USAGE**

Dexrazoxane for injection 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/m<sup>2</sup> and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy (see WARNINGS).

## **CONTRAINDICATIONS**

Dexrazoxane for injection should not be used with chemotherapy regimens that do not contain an anthracycline.

## **WARNINGS**

Dexrazoxane for injection may add to the myelosuppression caused by chemotherapeutic agents.

There is some evidence that the use of dexrazoxane concurrently with the initiation of fluorouracil, doxorubicin and cyclophosphamide (FAC) therapy interferes with the antitumor efficacy of the regimen, and this use is not recommended. In the largest of three breast cancer trials, patients who received dexrazoxane starting with their first cycle of FAC therapy had a lower response rate (48% vs. 63%; p = 0.007) and shorter time to progression than patients who did not receive dexrazoxane (see CLINICAL PHARMACOLOGY: Clinical Studies). Therefore, dexrazoxane for injection should only be used in those patients who have received a cumulative doxorubicin dose of 300 mg/m<sup>2</sup> and are continuing with doxorubicin therapy.

Although clinical studies have shown that patients receiving FAC with dexrazoxane for injection may receive a higher cumulative dose of doxorubicin before experiencing cardiac toxicity than patients receiving FAC without dexrazoxane for injection, the use of dexrazoxane for injection in patients who have already received a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup> without dexrazoxane for injection, does not eliminate the potential for anthracycline induced cardiac toxicity. Therefore, cardiac function should be carefully monitored.

### **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 for injection in combination with chemotherapy. Dexrazoxane for injection is not indicated for use in pediatric patients. Some adult patients who received dexrazoxane for injection 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 acute myeloid leukemia) 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.

### **Use in Pregnancy**

Dexrazoxane for injection can cause fetal harm when administered to pregnant women. There is no adequate information about the use of dexrazoxane for injection in pregnant women. In animal studies in rats and rabbits, dexrazoxane administration during the period of organogenesis was embryotoxic and teratogenic at doses significantly lower than the clinically recommended dose (see PREGNANCY). If

this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

## **PRECAUTIONS**

### **General**

Doxorubicin should not be given prior to the intravenous injection of dexrazoxane.

Dexrazoxane for injection should be given by slow I.V. push or rapid drip intravenous infusion from a bag. Doxorubicin should be given within 30 minutes after beginning the infusion with dexrazoxane for injection. (See DOSAGE AND ADMINISTRATION.)

As dexrazoxane for injection will always be used with cytotoxic drugs, patients should be monitored closely. While the myelosuppressive effects of dexrazoxane for injection at the recommended dose are mild, additive effects upon the myelosuppressive activity of chemotherapeutic agents may occur.

### **Patients with Moderate or Severe Renal Insufficiency**

Greater exposure to dexrazoxane may occur in patients with compromised renal function. The dexrazoxane for injection dose should be reduced by 50% in patients with creatinine clearance values < 40 mL/min (see DOSAGE AND ADMINISTRATION).

### **Laboratory Tests**

As dexrazoxane for injection may add to the myelosuppressive effects of cytotoxic drugs, frequent complete blood counts are recommended. (See ADVERSE REACTIONS.)

### **Drug Interactions**

Dexrazoxane for injection does not influence the pharmacokinetics of doxorubicin.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

(See WARNINGS section for information on human carcinogenicity) - No long-term carcinogenicity studies have been carried out with dexrazoxane in animals. Nevertheless, 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 in the Ames test but was found to be clastogenic to human lymphocytes *in vitro* and to mouse bone marrow erythrocytes *in vivo* (micronucleus test).

The possible adverse effects of dexrazoxane for injection on the fertility of humans and experimental animals, male or female, have not been adequately studied. Testicular atrophy was seen with dexrazoxane administration at doses as low as 30 mg/kg weekly for 6 weeks in rats (1/3 the human dose on a mg/m<sup>2</sup> basis) and as low as 20 mg/kg weekly for 13 weeks in dogs (approximately equal to the human dose on a mg/m<sup>2</sup> basis).

### **Pregnancy**

Teratogenic Effects. Pregnancy Category D

Dexrazoxane was toxic to pregnant rats at doses of 2 mg/kg (1/40 the human dose on a mg/m<sup>2</sup> basis) and embryotoxic and teratogenic at 8 mg/kg (approximately 1/10 the human dose on a mg/m<sup>2</sup> basis) when given daily to pregnant rats during the period of organogenesis. Teratogenic effects in the rat included imperforate anus, microphthalmia, and anophthalmia. In offspring allowed to develop to maturity, fertility was impaired in the male and female rats treated in utero during organogenesis at 8 mg/kg. In rabbits, doses of 5 mg/kg (approximately 1/10 the human dose on a mg/m<sup>2</sup> basis) daily during the period of organogenesis caused maternal toxicity and doses of 20 mg/kg (1/2 the human dose on a mg/m<sup>2</sup> basis) were embryotoxic and teratogenic. Teratogenic effects in the rabbit included 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. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient

should be apprised of the potential hazard to a fetus (see WARNINGS).

### Nursing Mothers

It is not known whether dexrazoxane is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dexrazoxane, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness of dexrazoxane in pediatric patients have not been established.

### Geriatric Use

Clinical studies of dexrazoxane for injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, elderly patients should be treated with caution due to the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

## ADVERSE REACTIONS

Dexrazoxane for injection at a dose of 500 mg/m<sup>2</sup> has been administered in combination with FAC in randomized, placebo-controlled, double-blind studies to patients with metastatic breast cancer. The dose of doxorubicin was 50 mg/m<sup>2</sup> in each of the trials. Courses were repeated every three weeks, provided recovery from toxicity had occurred. Table 3 below lists the incidence of adverse experiences for patients receiving FAC with either dexrazoxane for injection or placebo in the breast cancer studies. Adverse experiences occurring during courses 1 through 6 are displayed for patients receiving dexrazoxane for injection 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 for injection or placebo with FAC are also displayed (columns 2 and 4, respectively).

**Table 3**

Adverse Experience	Percentage (%) of Breast Cancer Patients with Adverse Experience			
	FAC + Dexrazoxane		FAC + Placebo	
	Courses 1 to 6 N = 413	Courses ≥ 7 N = 102	Courses 1 to 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

The adverse experiences listed above are likely attributable to the FAC regimen with the exception of pain on injection that was observed mainly on the dexrazoxane for injection arm.

### Myelosuppression

Patients receiving FAC with dexrazoxane for injection experienced more severe leukopenia, granulocytopenia and thrombocytopenia at nadir than patients receiving FAC without dexrazoxane for injection, but recovery counts were similar for the two groups of patients.

### Hepatic and Renal

Some patients receiving FAC + dexrazoxane for injection or FAC + placebo experienced marked abnormalities in hepatic or renal function tests, but the frequency and severity of abnormalities in bilirubin, alkaline phosphatase, BUN, and creatinine were similar for patients receiving FAC with or without dexrazoxane for injection.

### OVERDOSAGE

There have been no instances of drug overdose in the clinical studies sponsored by the National Cancer Institute. The maximum dose administered during the cardioprotective trials was 1000 mg/m<sup>2</sup> every 3 weeks.

Disposition studies with dexrazoxane for injection 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.

There is no known antidote for dexrazoxane. Instances of suspected overdose should be managed with good 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.

### DOSAGE AND ADMINISTRATION

The recommended dosage ratio of dexrazoxane for injection:doxorubicin is 10:1 (e.g., 500 mg/m<sup>2</sup> dexrazoxane for injection:50 mg/m<sup>2</sup> doxorubicin). In patients with moderate to severe renal dysfunction (creatinine clearance values < 40 mL/min), the recommended dosage ratio of dexrazoxane for injection:doxorubicin is 5:1 (e.g., 250 mg/m<sup>2</sup> dexrazoxane for injection:50 mg/m<sup>2</sup> doxorubicin). Creatinine clearance can be determined from a 24-hour urinary creatinine collection or estimated using the Crockroft-Gault equation (assuming stable renal function):

$$\text{Males: } \quad \text{CL}_{\text{CR}} = \frac{\text{body weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: } \quad \text{CL}_{\text{CR}} = \left[ \frac{\text{body weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}} \right] \times 0.85$$

Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the dexrazoxane for injection dosage should be proportionately reduced (maintaining the 10:1 ratio) in

patients with hepatic impairment.

Dexrazoxane for injection must be reconstituted with 0.167 Molar (M/6) sodium lactate injection, USP, to give a concentration of 10 mg dexrazoxane for injection for each mL of sodium lactate. The reconstituted solution should be given by slow I.V. push or rapid drip intravenous infusion from a bag. After completing the infusion of dexrazoxane for injection, and prior to a total elapsed time of 30 minutes (from the beginning of the dexrazoxane for injection infusion), the intravenous injection of doxorubicin should be given.

Reconstituted dexrazoxane for injection, when transferred to an empty infusion bag, is stable for 6 hours from the time of reconstitution when stored at controlled room temperature, 20° to 25°C (68° to 77°F) or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

The reconstituted dexrazoxane for injection solution may be diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a concentration range of 1.3 to 5 mg/mL in intravenous infusion bags. The resultant solutions are stable for 6 hours when stored at controlled room temperature, 20° to 25°C (68° to 77°F) or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

### **Incompatibility**

Dexrazoxane for injection should not be mixed with other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### **Handling and Disposal**

Caution in the handling and preparation of the reconstituted solution must be exercised and the use of gloves is recommended. If dexrazoxane for injection powder or solutions contact the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures normally used for proper handling and disposal of anticancer drugs should be considered for use with dexrazoxane for injection. Several guidelines on this subject have been published.<sup>1-4</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

### **HOW SUPPLIED**

Dexrazoxane for Injection is available in the following strengths as sterile, pyrogen-free lyophilizates.

NDC 67457-207-25

250 mg single-dose vial with a green flip-top seal, packaged in single vial packs. (This package also contains a 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP.)

NDC 67457-208-50

500 mg single-dose vial with a blue flip-top seal, packaged in single vial packs. (This package also contains a 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP.)

**Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]** Reconstituted solutions of dexrazoxane for injection are stable for 6 hours at controlled room temperature or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

### **REFERENCES**

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. [http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html).
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs.

*Am J Health-Syst Pharm.* 2006; 63:1172-1193.

4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2<sup>nd</sup> ed.). Pittsburgh, PA: Oncology Nursing Society.

Manufactured for:

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Rockford, IL 61103 U.S.A.

Manufactured by:

**Gland Pharma Limited**  
D.P. Pally, Dundigal Post  
Hyderabad-500 043, India

M.L.: 103/AP/RR/97/F/R

REVISED SEPTEMBER 2012

MI:DEXRIJ:R2

**PRINCIPAL DISPLAY PANEL - 250 mg**

**NDC 67457-207-25**

**Dexrazoxane for Injection**

**250 mg and**

**0.167M (M/6)**

**Sodium Lactate Injection, USP**

Sterile, pyrogen-free lyophilizate

**For Intravenous Use Only**

**Rx only**

**1 x 250 mg single dose vial dexrazoxane**

**1 x 25 mL vial sodium lactate injection, USP as diluent**

**Each vial contains:**

Dexrazoxane hydrochloride equivalent  
to 250 mg dexrazoxane.

The pH is adjusted with hydrochloric  
acid, NF.

This package also contains one 25 mL  
vial of 0.167M (M/6) sodium lactate  
injection, USP, as diluent.

Upon reconstitution with 25 mL vial of  
0.167M (M/6) sodium lactate injection,  
USP, the pH of the resultant solution is  
3.5 to 5.5.

Reconstituted solutions are stable for 6  
hours at controlled room temperature  
or under refrigeration, 2° to 8°C (36° to  
46°F).

Discard unused solutions.

**Usual Dosage:** See accompanying  
prescribing information.

**Store at 20° to 25°C (68° to 77°F).**

**[See USP Controlled Room  
Temperature.]**

Manufactured for:

**Mylan Institutional LLC**

Rockford, IL 61103 U.S.A.

Made in India

Code No.: AP/DRUGS/103/97

MI:207:2KC:R4

**Mylan.com**



**PRINCIPAL DISPLAY PANEL - 500 mg**

**NDC 67457-208-50**

**Dexrazoxane for Injection**

**500 mg and**

**0.167M (M/6)**

**Sodium Lactate Injection, USP**

Sterile, pyrogen-free lyophilizate

**For Intravenous Use Only**

**Rx only**

**1 x 500 mg single dose vial dexrazoxane**

**1 x 50 mL vial sodium lactate injection, USP as diluent**

**Each vial contains:**

Dexrazoxane hydrochloride equivalent to

500 mg dexrazoxane.

The pH is adjusted with hydrochloric acid, NF.

This package also contains one 50 mL

vial of 0.167M (M/6) sodium lactate injection, USP, as diluent.

Upon reconstitution with 50 mL vial of 0.167M (M/6) sodium lactate injection, USP, the pH of the resultant solution is 3.5 to 5.5.

Reconstituted solutions are stable for 6 hours at controlled room temperature or under refrigeration, 2° to 8°C (36° to 46°F).

Discard unused solutions.

**Usual Dosage:** See accompanying prescribing information.

**Store at 20° to 25°C (68° to 77°F).  
[See USP Controlled Room Temperature.]**

Manufactured for:  
**Mylan Institutional LLC**  
Rockford, IL 61103 U.S.A.

Made in India  
Code No.: AP/DRUGS/103/97

MI:208:2KC:R4

**Mylan.com**



# DEXRAZOXANE HYDROCHLORIDE

dexrazoxane kit

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG LABEL	<b>Item Code (Source)</b>	NDC:67457-207
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## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-207-25	1 in 1 PACKAGE		

## Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	25 mL
Part 2	1 VIAL	25 mL

## Part 1 of 2

### DEXRAZOXANE HYDROCHLORIDE

dexrazoxane injection, powder, lyophilized, for solution

## Product Information

<b>Item Code (Source)</b>	NDC:67457-204	
<b>Route of Administration</b>	INTRAVENOUS	<b>DEA Schedule</b>

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXRAZO XANE HYDRO CHLORIDE (DEXRAZO XANE)	DEXRAZO XANE	250 mg in 25 mL

## Inactive Ingredients

Ingredient Name	Strength
HYDRO CHLORIC ACID	

## Product Characteristics

<b>Color</b>	WHITE (whitish crystalline powder)	<b>Score</b>	
<b>Shape</b>		<b>Size</b>	
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-204-25	25 mL in 1 VIAL, SINGLE-DOSE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200752	11/14/2012	

## Part 2 of 2

### SODIUM LACTATE

sodium lactate injection, solution

## Product Information

Item Code (Source)	NDC:67457-205	
Route of Administration	INTRAVENOUS	DEA Schedule

## Inactive Ingredients

Ingredient Name	Strength
SODIUM LACTATE	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-205-25	25 mL in 1 VIAL		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200752	11/14/2012	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200752	11/14/2012	

## DEXRAZOXANE HYDROCHLORIDE

dexrazoxane kit

## Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:67457-208
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## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-208-50	1 in 1 PACKAGE		

## Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	50 mL
Part 2	1 VIAL	50 mL

## Part 1 of 2

### DEXRAZOXANE HYDROCHLORIDE

dexrazoxane injection, powder, lyophilized, for solution

## Product Information

Item Code (Source)	NDC:67457-209	
Route of Administration	INTRAVENOUS	DEA Schedule

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXRAZO XANE HYDRO CHLORIDE (DEXRAZO XANE)	DEXRAZO XANE	500 mg in 50 mL

## Inactive Ingredients

Ingredient Name	Strength
HYDRO CHLORIC ACID	

## Product Characteristics

Color	WHITE (whitish crystalline powder)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-209-50	50 mL in 1 VIAL, SINGLE-DOSE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200752	11/14/2012	

## Part 2 of 2

### SODIUM LACTATE

sodium lactate injection, solution

**Product Information**

<b>Item Code (Source)</b>	NDC:67457-205	
<b>Route of Administration</b>	INTRAVENOUS	<b>DEA Schedule</b>

**Inactive Ingredients**

<b>Ingredient Name</b>	<b>Strength</b>
SODIUM LACTATE	

**Packaging**

<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:67457-205-50	50 mL in 1 VIAL		

**Marketing Information**

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA200752	11/14/2012	

**Marketing Information**

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA200752	11/14/2012	

**Labeler** - Mylan Institutional LLC (790384502)

Revised: 9/2012

Mylan Institutional LLC