

**DEXRAZOXANE - dexrazoxane for injection injection, powder, lyophilized, for solution**  
**Gland Pharma Limited**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DEXRAZOXANE FOR INJECTION safely and effectively. See Full Prescribing Information for DEXRAZOXANE FOR INJECTION.

**DEXRAZOXANE for injection for intravenous use**

**Initial U.S. Approval: 1995**

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

Dexrazoxane for Injection is a cytoprotective agent 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. Do not use Dexrazoxane for Injection with doxorubicin initiation. (1)

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

- Reconstitute vial contents and dilute before use. (2.3)
- Administer Dexrazoxane for Injection by intravenous infusion over 15 minutes.
- DO NOT ADMINISTER VIA AN INTRAVENOUS PUSH. (2.1,2.3)
- The recommended dosage ratio of Dexrazoxane for Injection to doxorubicin is 10:1 (e.g., 500 mg/m<sup>2</sup> Dexrazoxane for Injection to 50 mg/m<sup>2</sup> doxorubicin). Do not administer doxorubicin before Dexrazoxane. (2.1)
- Reduce dose by 50% for patients with creatinine clearance <40 mL/min. (2.2, 8.7)

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

500 mg single dose vials as sterile, pyrogen-free lyophilized. (3)

----- **CONTRAINDICATIONS** -----

Dexrazoxane for Injection should not be used with non-anthracycline chemotherapy regimens. (4)

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

- Myelosuppression: Dexrazoxane for Injection may increase the myelosuppressive effects of chemotherapeutic agents. Perform hematological monitoring. (5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise female patients of reproductive potential of the potential hazard to the fetus. (5.5, 8.1)

----- **ADVERSE REACTIONS** -----

In clinical studies, Dexrazoxane for Injection was administered to patients also receiving chemotherapeutic agents for cancer. Pain on injection was observed more frequently in patients receiving Dexrazoxane for Injection versus placebo. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Gland Pharma at 864-879-9994 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

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

- Nursing Mothers: Discontinue drug or nursing. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 12/2016**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS & 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. Do not use with the initiation of doxorubicin therapy [see Warnings and Precautions (5.2)].

### **2 DOSAGE & ADMINISTRATION**

#### **2.1 Recommended Dose**

Administer Dexrazoxane for Injection via intravenous infusion over 15 minutes. DO NOT ADMINISTER VIA AN INTRAVENOUS PUSH.

The recommended dosage ratio of Dexrazoxane for Injection to doxorubicin is 10:1 (e.g., 500 mg / m<sup>2</sup> Dexrazoxane for Injection to 50 mg / m<sup>2</sup> doxorubicin). Do not administer doxorubicin before Dexrazoxane for Injection. Administer doxorubicin within 30 minutes after the completion of Dexrazoxane for Injection infusion.

## 2.2 Dose Modifications

### *Dosing in Patients with Renal Impairment*

Reduce Dexrazoxane for Injection dosage in patients with moderate to severe renal impairment (creatinine clearance values less than 40 mL/min) by 50% (Dexrazoxane for Injection to doxorubicin ratio reduced to 5:1; such as 250 mg/m<sup>2</sup> Dexrazoxane for Injection to 50 mg/m<sup>2</sup> doxorubicin) [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

### *Dosing in Patients with Hepatic Impairment*

Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, reduce the Dexrazoxane for Injection dosage proportionately (maintaining the 10:1 ratio) in patients with hepatic impairment.

## 2.3 Preparation and Administration

### Preparation and Handling of Infusion Solution

Reconstitute Dexrazoxane for Injection with Sterile Water for Injection, USP. Reconstitute with 50 mL for a Dexrazoxane for Injection 500 mg vial to give a concentration of 10 mg/mL. Dilute the reconstituted solution further with Lactated Ringer's Injection, USP to a concentration of 1.3 to 3.0 mg/mL in intravenous infusion bags for intravenous infusion.

Following reconstitution with Sterile Water for Injection, USP, Dexrazoxane for Injection is stable for 30 minutes at room temperature or if storage is necessary, up to 3 hours from the time of reconstitution when stored under refrigeration, 2° to 8°C (36° to 46°F). The pH of the resultant solution is 1.0 to 3.0. DISCARD UNUSED SOLUTIONS. The diluted infusion solutions are stable for one hour at room temperature or if storage is necessary, up to 4 hours when stored under refrigeration, 2° to 8°C (36° to 46°F). The infusion solutions have a pH of 3.5 to 5.5. DISCARD UNUSED SOLUTIONS.

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

Use caution when handling and preparing the reconstituted solution. The use of gloves is recommended. If Dexrazoxane for Injection powder or solutions contact the skin or mucosae, wash exposed area immediately and thoroughly with soap and water. Follow special handling and disposal procedures<sup>1</sup>.

### Administration

Do not mix Dexrazoxane for Injection with other drugs.

Administer the final diluted solution of Dexrazoxane for Injection 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 Dexrazoxane for Injection infusion.

## 3 DOSAGE FORMS & STRENGTHS

Dexrazoxane for Injection is available in 500 mg single dose vials as sterile, pyrogen-free lyophilized.

## 4 CONTRAINDICATIONS

Do not use Dexrazoxane for Injection with non-anthracycline chemotherapy regimens.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Myelosuppression

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

a complete blood count prior to and during each course of therapy, and administer Dexrazoxane for Injection and chemotherapy only when adequate hematologic parameters are met.

## 5.2 Concomitant Chemotherapy

Only use Dexrazoxane for Injection in those patients who have received a cumulative doxorubicin dose of 300 mg/m<sup>2</sup> and are continuing with doxorubicin therapy. Do not use with chemotherapy initiation as Dexrazoxane for Injection 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 for Injection starting with their first cycle of FAC therapy, patients who were randomized to receive Dexrazoxane for Injection 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 Dexrazoxane for Injection 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). In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated 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 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. Long-term administration of razoxane to rodents was associated with the development of malignancies [see *Nonclinical Toxicology (13.1)*].

## 5.5 Embryo-Fetal Toxicity

Dexrazoxane for Injection can cause fetal harm when administered to pregnant women. Dexrazoxane administration during the period of organogenesis resulted in maternal toxicity, embryotoxicity and teratogenicity in rats and rabbits at doses significantly lower than the clinically recommended dose [see *Use in Specific Populations (8.1)*]. 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.

Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception during treatment [see *Use in Specific Populations (8.6)*].

# 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.

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 FAC chemotherapy regimen with or without Dexrazoxane for Injection. The dose of doxorubicin was 50 mg/m<sup>2</sup> 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 for Injection experienced more severe leukopenia, granulocytopenia, and thrombocytopenia than patients receiving FAC without Dexrazoxane for Injection [see *Warnings and Precautions (5.1)*].

Table 1 below lists the incidence of adverse reactions 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).

The adverse reactions listed below in Table.1 demonstrate that the frequency of adverse reaction “Pain on Injection” has been greater for Dexrazoxane for Injection arm, as compared to placebo.

**Table 1**

Adverse Reaction	Percentage (%) of Breast Cancer Patients With Adverse Reaction			
	FAC + Dexrazoxane for Injection		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

No drug interactions have been identified [*see Clinical Pharmacology (12.3)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category D

#### *Risk Summary*

Dexrazoxane for Injection can cause fetal harm when administered to pregnant women. Dexrazoxane administration resulted in maternal toxicity, embryotoxicity and teratogenicity in rats and rabbits at doses significantly lower than the clinically recommended dose. 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 and Precautions (5.5)*].

#### *Animal Data*

Dexrazoxane resulted in maternal toxicity in rats at doses of  $\geq 2$  mg/kg (1/40 the human dose on a mg/m<sup>2</sup> basis) and embryotoxicity and teratogenicity 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  $\geq 5$  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.

### **8.3 Nursing Mothers**

It is not known whether dexrazoxane or its metabolites are 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.

### **8.4 Pediatric Use**

The safety and effectiveness of dexrazoxane in pediatric patients have not been established [*see Warnings and Precautions (5.4)*].

### **8.5 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, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### **8.6 Females of Reproductive Potential**

#### *Contraception*

Dexrazoxane for Injection can cause fetal harm when administered during pregnancy. Advise female patients of reproductive potential to use highly effective contraception during treatment [*see Use in Specific Populations (8.1)*].

## 8.7 Renal Impairment

Greater exposure to dexrazoxane may occur in patients with compromised renal function. Reduce the Dexrazoxane for Injection dose by 50% in patients with creatinine clearance values <40 mL/min [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

There are no data on overdosage in the cardioprotective trials; the maximum dose administered during the cardioprotective trials was 1000 mg/m<sup>2</sup> every three weeks.

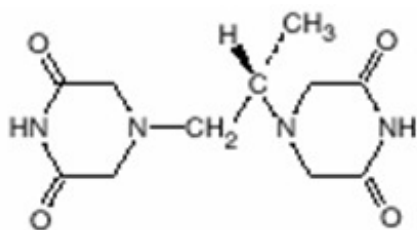
Disposition studies with Dexrazoxane for Injection have not been conducted in cancer patients undergoing dialysis, but retention of a significant dose fraction (>0.4) of the unchanged drug in the plasma pool, minimal tissue partitioning or binding, and availability of greater than 90% of the systemic 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.

## 11 DESCRIPTION

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

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



C<sub>11</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> M.W.268.28

Dexrazoxane, an 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 pKa is 2.1. Dexrazoxane has an octanol/water partition coefficient of 0.025 and degrades rapidly above a pH of 7.0.

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 50 mL of Sterile Water for Injection, USP, each mL contains: 10 mg dexrazoxane. The pH of the resultant solution is 1.0 to 3.0.

The reconstituted Dexrazoxane for Injection solutions prepared from Sterile Water for Injection, USP,

are intended for further dilution with Lactated Ringer's Injection, USP, for rapid intravenous drip infusion. DO NOT ADMINISTER VIA AN INTRAVENOUS PUSH [see Dosage and Administration (2.1, 2.3)].

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism by which Dexrazoxane for Injection exerts its cytoprotective activity 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 thought to be responsible, in part, for anthracycline-induced cardiomyopathy.

### 12.3 Pharmacokinetics

The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. 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 µg/mL at 15- minute after intravenous administration of 500 mg/m<sup>2</sup> dose of Dexrazoxane for Injection over 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 2:

**Table 2: SUMMARY OF MEAN (% CV<sup>a</sup>) DEXRAZOXANE PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF 10:1 OF DEXRAZOXANE FOR INJECTION: DOXORUBICIN**

Dose Doxirubicin (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> )	<sup>b</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)	-----	22.0 (55)

<sup>a</sup> Coefficient of variation

<sup>b</sup> Steady-state volume of distribution

#### *Distribution*

Following a rapid distributive phase (0.2 to 0.3 hours), dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated mean steady-state volume of distribution of dexrazoxane is 22.4 L/m<sup>2</sup> after 500 mg/m<sup>2</sup> of Dexrazoxane for Injection dose followed by 50 mg/m<sup>2</sup> of doxorubicin, suggesting distribution throughout total body water (25 L/m<sup>2</sup>).

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

#### *Metabolism*

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.

#### *Excretion*

Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of a 500 mg/m<sup>2</sup> dose of Dexrazoxane for Injection was excreted in the urine. Renal clearance averages 3.35 L/h/m<sup>2</sup> after the 500 mg/m<sup>2</sup> Dexrazoxane for Injection dose followed by 50 mg/m<sup>2</sup> of doxorubicin.

#### *Specific Populations*

##### *Pediatric*

Pharmacokinetics following Dexrazoxane for Injection administration have not been evaluated in pediatric patients.

##### *Effect of Renal Impairment*

The pharmacokinetics of dexrazoxane were assessed following a single 15-minute IV infusion of 150 mg/m<sup>2</sup> of Dexrazoxane for Injection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean AUC<sub>0-inf</sub> value was two-fold greater in subjects with moderate (CL<sub>CR</sub> 30-50 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 *Use in Specific Populations (8.7) and Dosage and Administration (2.2)*].

##### *Effect of Hepatic Impairment*

Pharmacokinetics following Dexrazoxane for Injection administration 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 (2.2)*].

##### *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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility**

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 [see *Warnings and Precautions (5.4)*].

Dexrazoxane was not mutagenic in the bacterial reverse mutation (Ames) test, but was found to be clastogenic to human lymphocytes in vitro and to mouse bone marrow erythrocytes in vivo (micronucleus test).

Dexrazoxane for Injection has the potential to impair fertility in male patients based on effects in repeat-dose toxicology studies. 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).

## **14 CLINICAL STUDIES**

The ability of Dexrazoxane for Injection to prevent/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 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 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; however, in the largest study, patients with advanced breast cancer receiving FAC with Dexrazoxane for Injection 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 for Injection after a cumulative dose of doxorubicin above 300 mg/m<sup>2</sup>. Retrospective historical analyses showed that the risk of experiencing a cardiac event (see Table 3 for definition) at a cumulative dose of doxorubicin above 300 mg/m<sup>2</sup> was greater in the patients who did not receive Dexrazoxane for Injection beginning with their seventh course of FAC than in the patients who did receive Dexrazoxane for Injection (HR=13.08; 95% CI: 3.72, 46.03; p<0.001). Overall, 3% of patients treated with Dexrazoxane for Injection developed CHF compared with 22% of patients not receiving Dexrazoxane for Injection.

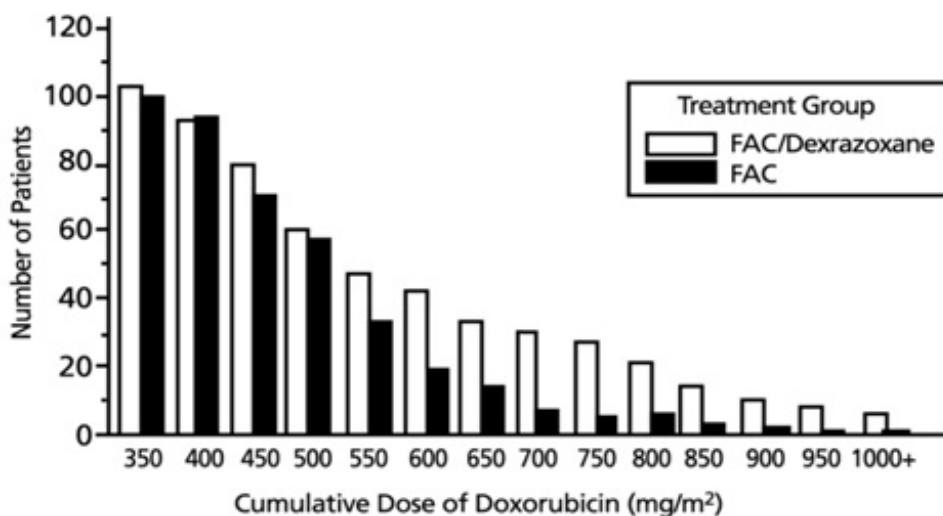
**Table 3: Definition of Cardiac Events:**

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 for Injection 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

Dexrazoxane for injection is available in the following strength as sterile, pyrogen-free lyophilized.

NDC 68083-195-01

500 mg single dose vial with a blue flip-top seal, packaged in single vial packs.

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

Follow special handling and disposal procedures.

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Myelosuppression

Treatment with Dexrazoxane for Injection is associated with leukopenia, neutropenia, and thrombocytopenia. Perform hematological monitoring [see *Warnings and Precautions (5.1), (5.6)*].

### 17.2 Embryo-Fetal Toxicity

Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential that Dexrazoxane for Injection can cause fetal harm and to use highly effective contraception during treatment [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.6)*].

## PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 68083-195-01

Dexrazoxane for Injection 500 mg/50 mL vial

FOR INTRAVENOUS USE ONLY

Single Dose Vial

Vial Label

NDC 68083-195-01	Rx Only
SINGLE DOSE VIAL	
<b>Dexrazoxane for Injection 500 mg*/vial</b>	
Sterile, Pyrogen-Free Lyophilized	
FOR INTRAVENOUS USE ONLY	
<small>*Each vial contains Dexrazoxane hydrochloride equivalent to 500 mg Dexrazoxane. The pH is adjusted with Hydrochloric acid, NF. Upon reconstitute with 50 mL of Sterile water for Injection, USP, the pH of resultant solution is 1.0 to 3.0. Reconstituted solutions are stable for 30 minutes at room temperature or if storage is necessary, up to 3 hours from the time of reconstitution when stored under refrigeration, 2° to 8°C (36° to 46°F). Further dilution with Lactated Ringer's Injection, USP, is necessary prior to administration via IV drip. DO NOT ADMINISTER RECONSTITUTED SOLUTION DIRECTLY Discard unused solution. <b>Dosage and Use:</b> See accompanying prescribing information. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].</small>	
<small>Manufactured by: <b>GLAND PHARMA LIMITED</b> DP: Pally, Hyderabad - 500043, INDIA. M.L.No.: 103/AP/RR/97/F/R</small>	
LAB-XXXXXX-00	
	
Lot:	Un varnish area 18 x 19 mm
Exp:	

NDC 68083-195-01

Dexrazoxane for Injection 500 mg/50 mL vial  
 FOR INTRAVENOUS USE ONLY  
 Single Dose Vial  
 Carton Label



**DEXRAZOXANE**

dexrazoxane for injection injection, powder, lyophilized, for solution

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68083-195
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Route of Administration INTRAVENOUS

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DEXRAZOXANE HYDROCHLORIDE (UNII: 5346058Q7S) (DEXRAZOXANE - UNII:048L81261F)	DEXRAZOXANE	500 mg in 50 mL

### Inactive Ingredients

Ingredient Name	Strength
HYDROCHLORIC ACID (UNII: QTT17582CB)	

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68083-195-01	01 in 1 CARTON	12/05/2016	
1		50 mL in 1 VIAL; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207321	12/05/2016	

**Labeler** - Gland Pharma Limited (918601238)

### Establishment

Name	Address	ID/FEI	Business Operations
Gland Pharma Limited		918601238	ANALYSIS(68083-195) , API MANUFACTURE(68083-195) , MANUFACTURE(68083-195) , PACK(68083-195)

Revised: 12/2016

Gland Pharma Limited