PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Dexrazoxane for injection

Sterile lyophilized Powder for Solution, 250 mg / vial, Intravenous Infusion

Cardioprotective Agent

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Date of Initial
Authorization:

MAY 23, 2025

Submission Control Number: 286896

RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Dexrazoxane for injection (dextrazoxane for injection) is indicated for:

- Reducing (preventing) the incidence and severity of cardiotoxicity associated with doxorubicin administration for the treatment of metastatic breast cancer in patients who have already experienced a partial response or at least maintained stable disease.

Dexrazoxane for Injection should be used only with chemotherapy regimens containing doxorubicin.

There is some evidence that the use of dexrazoxane concurrently with the initiation of fluorouracil, doxorubicin and cyclophosphamide (FAC) therapy interferes with the antitumour efficacy of the regimen, and this use is not recommended. Dexrazoxane for Injection should be used only after tolerance to a full dose doxorubicin has been established (see **7 WARNINGS AND PRECAUTIONS**).

1.1 Pediatrics

Pediatrics (< 18 years of age): Dexrazoxane for Injection is not indicated for use in patients below the age of 18 years (see **7.1 Special Populations**, **7.1.3 Pediatrics**).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of dexrazoxane for injection did not include sufficient numbers of subjects 65 and over to determine whether they respond differently from younger subjects (see **7.1 Special Populations**, **7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

- Dexrazoxane for Injection should not be used as a chemotherapeutic agent.
- Dexrazoxane for Injection is contraindicated in patients who have known hypersensitivity to dexrazoxane or any ingredient in the formulation or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- Do not use Dexrazoxane for Injection with non-anthracycline chemotherapy regimens.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Dexrazoxane for Injection is a potent drug and should be used only by physicians experienced with cancer chemotherapy drugs.

- **Myelosuppression: Dexrazoxane for Injection may increase the myelosuppressive effects of chemotherapeutic agents (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Immune, and Monitoring and Laboratory Tests).**
- **Embryo-Fetal Toxicity: Dexrazoxane for Injection can cause fetal harm. Advise female patients of reproductive potential of the potential hazard to the fetus (see 7.1 Special Populations, 7.1.1 Pregnant Women).**
- **Renal insufficiency: Dosage adjustment is recommended in patients with renal impairment (see 7 WARNINGS AND PRECAUTIONS, Renal and 4 DOSAGE AND ADMINISTRATION).**
- **Hepatic insufficiency: Dexrazoxane for Injection has not been studied in patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and Monitoring and Laboratory Tests).**
- **Dexrazoxane for Injection should not be administered in a dose that exceeds 500 mg/m^2.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Dexrazoxane for injection should be reconstituted with Sterile Water for Injection, USP to a concentration of 10 mg/mL. The reconstituted Dexrazoxane for Injection solution is intended for further dilution with Lactated Ringer's Injection, USP to a concentration range of 1.3 to 3.0 mg/mL before use according to the instructions given in section **4.3 Reconstitution**.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage ratio of dexrazoxane:doxorubicin is 10:1 (e.g. 500 mg/m^2 Dexrazoxane: 50 mg/m^2 doxorubicin) (see **7 WARNINGS AND PRECAUTIONS**).

Hepatic insufficiency: Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the Dexrazoxane for Injection dosage should be proportionately reduced in patients with hepatic impairment to maintain the 10:1 ratio of dexrazoxane:doxorubicin.

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

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

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

4.3 Reconstitution

Parenteral Products:

Recommended Diluent for Reconstitution: The reconstitution diluent Sterile Water for Injection, USP, has been studied for compatibility and stability with Dexrazoxane for Injection. Dexrazoxane for Injection should only be reconstituted with Water for Injection, USP. No other diluent should be used to reconstitute Dexrazoxane for Injection.

The reconstituted Dexrazoxane for Injection solution is intended for further dilution for rapid intravenous drip infusion. DO NOT ADMINISTER VIA INTRAVENOUS PUSH.

Reconstitute each vial with Sterile Water for Injection, USP, according to **Table 1**. The reconstituted Dexrazoxane for Injection prepared from Sterile Water for Injection, USP, 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. The pH of the resultant solution is 1.0 to 3.0. DISCARD UNUSED SOLUTIONS, (see **11 STORAGE, STABILITY AND DISPOSAL**).

All steps of dilution and administration must be conducted using non-PVC materials and containers.

Table 1 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
250 mg	25	25*	10

***Must be further diluted prior to administration**

Dilution following reconstitution: The resultant reconstituted Dexrazoxane for Injection solution prepared with Sterile Water for Injection, USP, MUST be further diluted with Lactated Ringer's Injection, USP, to a concentration range of 1.3 to 3.0 mg/mL in intravenous infusion bags for rapid intravenous drip infusion. The pH of the resultant solution is 3.5 to 5.5. The resultant solution is stable for one hour at room temperature or if storage is necessary up to 4 hours when stored under refrigeration, 2 to 8°C. DISCARD UNUSED SOLUTIONS (see **11 STORAGE, STABILITY AND DISPOSAL**).

Incompatibility: Unless specific compatibility data are available, Dexrazoxane for Injection should not be mixed with other drugs.

4.4 Administration

The reconstituted solution when further diluted with Lactated Ringer's Injection MUST be given by rapid drip intravenous infusion. DO NOT ADMINISTER VIA INTRAVENOUS PUSH. Administer the final diluted solution of Dexrazoxane for Injection over 15 minutes before the administration of doxorubicin. Administer doxorubicin within 30 minutes after the completion of Dexrazoxane for Injection infusion.

Dexrazoxane for Injection should be administered only after the tolerance of the patient to the full dose of doxorubicin-containing chemotherapeutic regimen has been determined.

Dexrazoxane for Injection should be given only when there is no need for dose reduction or dose delay, of the chemotherapeutic regimen due to myelosuppression or other toxicities, in two consecutive courses.

Dexrazoxane for Injection should be given only to patients who have already experienced partial response or at least maintained stable disease.

All steps of dilution and administration must be conducted using non-PVC materials and containers.

5 OVERDOSAGE

There have been no instances of drug overdose in the clinical studies sponsored by either Pharmacia Corporation or the National Cancer Institute, U.S.A. The maximum dose administered during the cardioprotection trials was 1000 mg/m^2 every three weeks.

Disposition studies with dexrazoxane for injection have not been conducted in cancer patients undergoing dialysis. However, 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 its toxicity and efficacy would be altered by its removal using conventional peritoneal or hemodialysis.

There is no known antidote. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized Powder for Solution 250 mg/vial	Hydrochloric acid

Dexrazoxane for injection is available in:

- 250 mg single dose vial, for reconstitution with recommended diluent.

Diluent not provided.

The 250 mg vial contains 250 mg of dexrazoxane; pH is adjusted with hydrochloric acid.

The final concentration of the reconstituted solution is 10 mg/mL. Vial stopper is not made with natural rubber latex.

Sterile, preservative-free, essentially free from visible particles

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX.**

General

Dexrazoxane for Injection should only be used in those patients who have received a cumulative doxorubicin dose of 300 mg/m^2 and are continuing with doxorubicin therapy.

Dexrazoxane for Injection should be administered only after the tolerance of the patient to the full

dose of doxorubicin-containing chemotherapeutic regimen has been determined. Dexrazoxane for Injection should be given only when there is no need for dose reduction or dose delay, of the chemotherapeutic regimen due to myelosuppression or other toxicities, in two consecutive courses.

It is important that physicians use the product according to the recommended dosage as indicated in the label (10:1 Ratio) as any other dosages outside label recommendations can potentially compromise the safety of the patient.

Currently, the only clinical experience with late administration is in patients who were crossed over from placebo and received dexrazoxane for injection after 6 courses of chemotherapy. Dexrazoxane for injection was found to retain its cardioprotective effect in these patients. However, an incidence of up to 20% of cardiovascular events was seen prior to the initiation of dexrazoxane for injection administration. Therefore, the administration of Dexrazoxane for Injection should not be delayed beyond the 7th course of therapy.

Carcinogenesis and Mutagenesis

Second primary malignancies: Secondary acute myeloid leukaemia (AML) / myelodysplastic syndrome (MDS) have been observed in paediatric patients with Hodgkin's disease or acute lymphoblastic leukaemia receiving dexrazoxane in combination with chemotherapy. Cases of AML have also been reported in adult breast cancer patients treated with dexrazoxane in combination with chemotherapy. Dexrazoxane for Injection is not indicated for use in patients below the age of 18 years.

Cardiovascular

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^2 without dexrazoxane for injection, does not eliminate the potential for anthracycline induced cardiac toxicity. Therefore, cardiac function should be carefully monitored.

Hematologic

Dexrazoxane for Injection may **add to** the myelosuppression caused by chemotherapeutic agents. Dexrazoxane for Injection may interfere with the antitumour activity of chemotherapeutic agents.

Combination of dexrazoxane with chemotherapy may lead to an increased risk of thromboembolism.

Hepatic/Biliary/Pancreatic

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. 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 (see **4 DOSAGE AND ADMINISTRATION**).

Immune

In controlled studies, a slightly higher incidence of infection associated with granulocytopenia occurred in patients receiving dexrazoxane for injection. 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 considered to be mild, additive effects upon the myelosuppressive activity of chemotherapeutic agents may occur.

Monitoring and Laboratory Tests

As Dexrazoxane for Injection may add to the myelosuppressive effects of cytotoxic drugs, frequent

complete blood counts, including one prior to each treatment, should be performed due to the possibility of additive myelosuppressive effects (see **7 WARNINGS AND PRECAUTIONS, Hematologic**, **Immune** and **8 ADVERSE REACTIONS**).

Patients should be monitored for cardiac function before and periodically during therapy to assess left ventricular ejection fraction (LVEF) (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**).

It is recommended that routine liver function tests be performed before each administration of dexrazoxane in patients with known liver function disorders (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **4 DOSAGE AND ADMINISTRATION**).

Since renal dysfunction may decrease the rate of elimination of dexrazoxane, patients with initial impaired renal function should be monitored for signs of haematological toxicity (See **7 WARNINGS AND PRECAUTIONS, Renal** and **4 DOSAGE AND ADMINISTRATION**).

Renal

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 **4 DOSAGE AND ADMINISTRATION**).

Reproductive Health: Female and Male Potential

There is no conclusive information about dexrazoxane adversely affecting human fertility.

Sensitivity/Resistance

Anaphylactic reaction including angioedema, skin reactions, bronchospasm, respiratory distress, hypotension and loss of consciousness have been observed in patients treated with dexrazoxane and anthracyclines.

7.1 Special Populations

7.1.1 Pregnant Women

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 **16 NON-CLINICAL TOXICOLOGY**).

Dexrazoxane for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women of child-bearing potential should be advised to practice effective contraception.

7.1.2 Breast-feeding

Mothers should be advised not to breastfeed while undergoing therapy with Dexrazoxane for Injection.

It is not known whether this drug 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, it is recommended that nursing be **discontinued during treatment**.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Dexrazoxane for Injection is not indicated for use in patients below the age of 18 years. Since dexrazoxane is a cytotoxic agent, with topoisomerase II inhibition activity, combination of dexrazoxane with chemotherapy may lead to an increased risk of second primary malignancy. In clinical trials, second primary malignancies, in particular acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), have been reported in paediatric patients with Hodgkin's disease and acute lymphoblastic leukaemia receiving chemotherapy regimens including several cytotoxics (e.g. etoposide, doxorubicin, cyclophosphamide).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of dexrazoxane for injection did not include sufficient numbers of subjects 65 and over to determine whether they respond differently from 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Not available.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Dexrazoxane for injection at a dose of 500 mg/m^2 has been administered in combination with fluorouracil, doxorubicin, and cyclophosphamide (FAC) or cyclophosphamide, doxorubicin and vincristine (CAV) in randomized placebo controlled double-blind studies to patients with either metastatic breast cancer (FAC) or extensive disease small cell lung cancer (CAV). The dose of doxorubicin was 50 mg/m^2 in each of the trials. Courses were repeated every three weeks provided recovery from toxicity had occurred. **Table 3** lists the incidence of clinical adverse experiences for patients receiving either dexrazoxane for injection or placebo in the breast cancer studies.

Table 3. – PERCENTAGE OF BREAST CANCER PATIENTS WITH ADVERSE EXPERIENCE

ADVERSE EXPERIENCE	FAC+ dexrazoxane for injection N = 244 (%)	FAC + PLACEBO N = 280 (%)
Alopecia	94	96
Nausea	82	89
Vomiting	63	77
Fatigue/Malaise	62	64
Anorexia	50	52
Stomatitis	36	45
Fever	35	33
Infection and/or Sepsis	31	28
Diarrhea	22	24
Neurotoxicity	16	13
Pain on Injection	11	4
Streaking/Erythema	7	5
Dysphagia	6	10
Phlebitis	5	5
Urticaria	4	2

ADVERSE EXPERIENCE	FAC+ dexrazoxane for injection N = 244 (%)	FAC+PLACEBO N = 280 (%)
Esophagitis	5	9
Hemorrhage	2	2
Extravasation	2	1
Recall Skin Reaction	1	2
CHF	1	5

The only adverse experience that was observed in 5% more patients on FAC + dexrazoxane for injection than on FAC + placebo was pain on injection. However, the early drop-out rate for patients receiving dexrazoxane for injection was higher than for patients receiving placebo.

Myelosuppression: Eighty-eight percent (88%) of breast cancer patients receiving FAC + 500 mg/m^2 dexrazoxane for injection and 85% of patients receiving FAC + placebo experienced Grade 3 or 4 granulocytopenia. Ten percent (10%) of patients receiving FAC + dexrazoxane for injection and 9% of patients receiving FAC + placebo experienced Grade 3 or 4 thrombocytopenia at some time while on study.

The median decline in hemoglobin levels from baseline was 2.6 g/dL for patients receiving FAC + dexrazoxane for injection or FAC + placebo.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The clinical trial adverse reaction data is not available.

8.3 Less Common Clinical Trial Adverse Reactions

The clinical trial adverse reaction data is not available.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

The clinical trial adverse reaction data is not available.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Hepatic and Renal: Very few patients receiving FAC + dexrazoxane for injection or FAC + placebo experienced marked abnormalities in hepatic or renal function tests; the frequency and severity of abnormalities in bilirubin, alkaline phosphatase, LDH, BUN, and creatinine levels were similar.

Post-Market Findings

The post-market abnormal laboratory findings data is not available.

8.5 Post-Market Adverse Reactions

The post-market adverse reaction data is not available.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Based on a kinetic study, dexrazoxane for injection does not appear to influence the pharmacokinetics of doxorubicin.

The use of Dexrazoxane for Injection concurrently with fluorouracil, doxorubicin and cyclophosphamide (FAC) therapy (a chemotherapy regimen) might interfere with the antitumour efficacy of the FAC.

9.3 Drug-Behavioural Interactions

There is no data on drug-behavioural interactions.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal product have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dexrazoxane is a cyclic derivative of EDTA which, unlike EDTA, readily penetrates cell membranes. Dexrazoxane was shown to be able to protect the myocardium from anthracycline-induced cardiotoxicity. The mechanism by which dexrazoxane exerts its cardioprotective activity is not fully understood. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to an open-ringed chelating agent which interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiotoxicity.

10.2 Pharmacodynamics

This information is not available.

10.3 Pharmacokinetics

Pharmacokinetic studies have been performed in advanced cancer patients with normal renal and hepatic function following administration of dexrazoxane for injection as a 15-minute intravenous infusion over a dose- range of 60 to 900 mg/m^2 with 60 mg/m^2 of doxorubicin, and at a fixed dose of 500 mg/m^2 with 50 mg/m^2 doxorubicin.

Absorption:

The mean peak plasma concentration of dexrazoxane at the end of the 15-minute infusion was 36.5 mcg/mL and was below the limit of quantitation (5 ng/mL) after 24 hours. The biphasic decay of the plasma concentration of dexrazoxane is best described by an empirical two-compartment open model.

Distribution:

Following a rapid distributive phase ($t½,\lambda_1$: ~0.2 to 0.3 hours), dexrazoxane reached post-distributive equilibrium by two to four hours. The estimates of the mean volume of the central compartment (V_c) and the distribution volume at steady-state (V_{ss}) were 12.9 and 25.6 L/m^2, respectively. This suggests minimal tissue uptake of dexrazoxane and its confinement in a volume equal to the total body water (25 L/m^2).

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

Metabolism:

Plasma clearance of Dexrazoxane for Injection is via both renal and nonrenal elimination. The nonrenal component is mainly metabolic. 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.

Elimination:

The means *(± sd; range)* of the terminal elimination half-life ($t½,\lambda_z$) and systemic clearance (CL_s) were 2.5 (± 0.4; 1.8 to 3.3) hours and 9.56 (± 3.56; 5.93 to 16.71) L/Hr/m^2, respectively. The coefficient of variation (%CV) in these estimates was generally less than 42%. Excellent proportionality between the area under the plasma dexrazoxane concentration-time curve (AUC) and administered dose, and no change in CL_s, t½, and V_{ss} indicate that its disposition kinetics are apparently dose-independent. The mean (± sd; range) urinary excretion (expressed as percent dose) for dexrazoxane was 37.0% (± 15.0; 17.1 to 61.2%).

Special Populations and Conditions

- **Renal Insufficiency:** The pharmacokinetics of dexrazoxane for injection were assessed following a single 15-minute intravenous infusion of 150 mg/m^2 of dexrazoxane in male and female subjects with varying degrees of renal dysfunction as determined by creatinine clearance (CL_{CR}) based on a 24-hour urinary creatinine collection. Dexrazoxane clearance was reduced in subjects with renal dysfunction. Compared with controls, the mean $AUC_{0\text{-inf}}$ value was two-fold greater in subjects with moderate (CL_{CR} 30-50 mL/min) to severe (CL_{CR} <30 mL/min) renal dysfunction. Modeling demonstrated that equivalent exposure ($AUC_{0\text{-inf}}$) could be achieved if dosing were reduced by 50% in subjects with creatinine clearance values < 40 mL/min compared with control subjects (CL_{CR} >80 mL/min).

11 STORAGE, STABILITY AND DISPOSAL

Unreconstituted Vials

Dexrazoxane for Injection lyophilized powder for injection should be stored at controlled room temperature, 15-25°C.

Reconstituted Solution

The reconstituted solution in Sterile Water for Injection is stable for 30 minutes at room temperature or a maximum of 3 hours under refrigeration, 2°-8°C (see **4.3 Reconstitution**).

Reconstituted and further Diluted Solution

The reconstituted solution when further diluted with Lactated Ringer's Injection is stable for 1 hour at room temperature or a maximum of 4 hours under refrigeration, 2°-8°C (see **4.3 Reconstitution**).

12 SPECIAL HANDLING INSTRUCTIONS

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 solution contacts 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. However, there is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Preparation and Handling

1. Preparation of the reconstituted solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel handling dexrazoxane solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If dexrazoxane solutions contact the skin or mucosa, the area should be washed with soap and water immediately.
3. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.
2. All needles, syringes, vials and other materials which have come in contact with dexrazoxane should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.
3. If incineration is not available, dexrazoxane may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the dexrazoxane, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution and disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination

Wear gloves, mask, protective clothing. Treat spilled liquid with sodium hypochlorite solution. Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Disposal of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

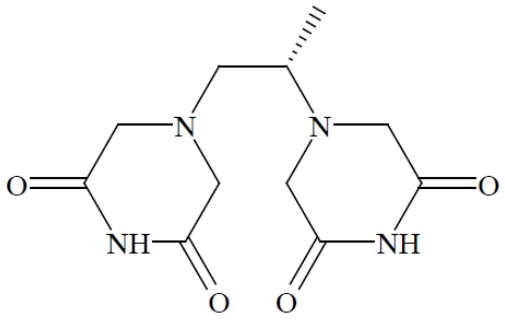
Drug Substance

Proper name: Dexrazoxane

Chemical name: (S)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione

Molecular formula and molecular mass: $C_{11}H_{16}N_4O_4$ and 268.28 g/mol

Structural formula:



Physicochemical properties: Dexrazoxane is white to off-white powder essentially free from visible contaminants

Melting Point: 191 °C to 193 °C

Specific Rotation: +10.0° to +13.0°

Hygroscopicity: Hygroscopicity was assessed using dynamic vapor sorption (DVS) and it was found that FP-048 is slightly hygroscopic at humidity levels >60% RH and gains ~0.5% by weight. The mass gained is readily lost upon returning the FP-048 to <60% RH. XRPD before and after treatment to a high humidity environment is unchanged.

Solubility: FP-048 is soluble in water at greater than 4 mg/mL at room temperature.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Prospective studies

The efficacy of dexrazoxane for injection in preventing/reducing the incidence and severity of doxorubicin-induced cardiomyopathy was demonstrated in a series of prospective 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. Cardiac function was assessed by measurement of the left ventricular ejection fraction (LVEF) utilizing resting multigated nuclear medicine (MUGA) scans and by clinical evaluations.

Amended randomized breast cancer studies

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^2 (six (6) courses of FAC) to receive FAC with open-label dexrazoxane for injection for each subsequent course. Most of these patients had already

experienced a partial or complete response or had stable disease.

14.2 Study Results

Prospective studies

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^2 and reached statistical significance in patients who received $\geq$ 400 mg/m^2 of doxorubicin. The studies also assessed the effect of the addition of dexrazoxane for injection on the antitumour efficacy of the chemotherapy regimens.

In one of the studies (the largest of the breast cancer studies) patients with advanced breast cancer receiving fluorouracil, Adriamycin and cyclophosphamide (FAC) with dexrazoxane for injection had a lower response rate and a shorter time to progression than patients on the control arm although the survival of the patients who did or did not receive dexrazoxane for injection with FAC was similar. More non-responders dropped out by course three in the dexrazoxane for injection arm. The non-responders correlated to dose delays due to additive myelotoxicity. It appears that dexrazoxane for injection may potentiate doxorubicin toxicity in some patients, thus causing increased early dropout rate or decreased dose-intensity.

Amended randomized breast cancer studies

Analyses of these amended studies indicate that significant though not complete cardioprotection can be obtained with the administration of dexrazoxane for injection only after the accumulated dose of 300 mg/m^2 of doxorubicin. In addition, the time to tumour progression and survival of these two groups of patients were also compared. Results demonstrate significantly longer overall survival for the group of patients who received dexrazoxane for injection starting with the seventh course of FAC treatment.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Toxicology studies were carried out in the mouse, rat and dog, with dexrazoxane alone and in combination with either doxorubicin or epirubicin, two of the most widely used antineoplastic anthracyclines, as well as with other antineoplastic drugs likely to be used in anthracycline-containing chemotherapeutic regimens.

Single intravenous doses of dexrazoxane of up to 1000 mg/kg in either saline or sodium lactate, were well tolerated in the mouse. In the rat, the LD_{50} of dexrazoxane was estimated to be greater than 1000 mg/kg. Acute toxic effects of single infusions of dexrazoxane at doses of 250, 500, 1000 or 2000 mg/kg were examined in the beagle dog. The 250 and 500 mg/kg doses were considered well tolerated in the dog. Cytoplasmic alterations were observed in the liver at the two highest doses and hemorrhage was noted in several tissues of the high dose dog. There was some evidence of granulocyte hypoplasia or erythroid hyperplasia in the high dose male.

In the mouse, the LD_{50} for doxorubicin alone was 16 and 23 mg/kg in males and females, respectively, whereas the LD_{50} for doxorubicin given in combination with dexrazoxane (20 to 1,

dexrazoxane:doxorubicin) was 25 and 26 mg/kg in males and females, respectively. The LD_{50} of epirubicin alone in male and female mice, were 26 and 28 mg/kg, respectively, whereas in combination with dexrazoxane, the LD_{50} were 30 and 34 mg/kg, respectively.

The pathologic changes found in the dexrazoxane:epirubicin treatment groups were consistent with anthracycline toxicity. Dexrazoxane had no appreciable effect on the acute toxicity of vincristine or cisplatin in the mouse.

The effects of dexrazoxane on the acute toxicity of doxorubicin were examined in the rat using doses of 3 to 12 mg/kg doxorubicin at ratios of 20 to 1, dexrazoxane:doxorubicin. The LD_{50} for doxorubicin alone were 12.5 and 15 mg/kg in males and females, respectively, and for the combination, 12 and 11.3 mg/kg. Dexrazoxane tended to exacerbate the lethality of doxorubicin at the higher doses (>9 mg/kg doxorubicin), but exhibited some protection against the gross pathologic effect of doxorubicin (small thymus, fluid in abdominal and thoracic cavities).

In the dog, the acute toxicity of dexrazoxane given 30 minutes prior to doxorubicin was studied at doses of 5, 10, 20 and 40 mg/kg dexrazoxane and 0.25, 0.5, 1.0 and 2.0 mg/kg doxorubicin. Doses up to 20 mg/kg were well tolerated with slight transient changes in haematology and clinical chemistry, but the highest dose was toxic. In combination with epirubicin or cisplatin, dexrazoxane did not affect the toxicity profile commonly seen with these two agents administered alone. Chronic toxicity studies were carried out in the, rat and beagle dog after intravenous courses of dexrazoxane both alone or in combination with doxorubicin or epirubicin for a total of 6 and 13 weeks.

Results showed that in the rat and dog, dexrazoxane (administered at 20 to 1 dose ratios) exhibited protection against doxorubicin-induced cardiotoxicity and epirubicin-induced renal tubulonephrosis, but did not affect the other commonly associated toxicities. Dexrazoxane was given intravenously at doses of 10, 20 and 40 mg/kg approximately 25 minutes before an intravenous dose of doxorubicin at 0.5, 1.0 and 2.0 mg/kg, respectively. Controls included dexrazoxane alone (40 mg/kg) and doxorubicin alone (2.0 mg/kg). Dexrazoxane alone had minimal effects, the most important of which was a decrease in testes and thymus weights which were not associated with histomorphological changes. Doxorubicin, either alone or together with dexrazoxane, caused anaemia, leukopenia, bone marrow depletion, thymus atrophy, hyperplasia of immature lymphocytes and lymphoid depletion of mesenteric lymph nodes. Doxorubicin caused renal tubulonephrosis which was prevented to a significant degree by dexrazoxane. Changes in serum chemistry in doxorubicin-treated rats were less severe in the rats given dexrazoxane with doxorubicin. Dexrazoxane also exhibited protection against doxorubicin-induced cardiotoxicity.

Epirubicin given intravenously at doses of 0.6, 1.2, and 2.4 mg/kg, caused anaemia, leukopenia, bone marrow depletion, testicular atrophy, renal tubulonephrosis and cardiotoxicity in the rat. Dexrazoxane (12, 24, and 48 mg/kg) exhibited some protection against the renal tubulonephrosis and cardiotoxicity induced by epirubicin, but did not affect the other toxicities of epirubicin appreciably.

Carcinogenicity: No long-term carcinogenicity studies have been carried out with dexrazoxane in animals.

Genotoxicity and Mutagenicity: Dexrazoxane was not mutagenic in the Ames test but was found to be clastogenic in human lymphocytes *in vitro* and to bone marrow erythrocytes in the mouse (micronucleus test). Dexrazoxane did not alter the mutagenic or the genotoxic properties of doxorubicin.

Secondary malignancies (primarily acute myeloid leukemia) have been reported in patients treated chronically with oral razoxane. Razoxane is the racemic mixture, of which dexrazoxane is the S(+)-enantiomer. 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, a 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.

Reproductive and Developmental Toxicology: Dexrazoxane was maternotoxic at dosages of 2 mg/kg and embryotoxic and teratogenic at 8 mg/kg when given daily to pregnant rats during the period of organogenesis. Teratogenic effects in the rat included imperforate anus, microphthalmia, and anophthalmia. In rabbits, dosages of 5 mg/kg daily during the period of organogenesis were maternotoxic and dosages of 20 mg/kg were embryotoxic and teratogenic. Teratogenic effects in the rabbit included several malformations as well as agenesis of the gallbladder and of the intermediate lobe of the lung.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ZINECARD® (250 mg / vial and 500 mg / vial), submission control 267046, Product Monograph, Pfizer Canada ULC (APR 11, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Dexrazoxane for injection

Read this carefully before you start taking **Dexrazoxane for Injection** and each time you get an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Dexrazoxane for Injection.**

Serious Warnings and Precautions

Dexrazoxane for Injection should only be given to you by healthcare professionals experienced in the use of cancer chemotherapy drugs.

- **Myelosuppression** (lower bone marrow action): Dexrazoxane for Injection can contribute to lower bone marrow action. This lowers the blood cell count in your body and can make your immune system more weak. This can make it easier for you to get sick or have an infection.
- **Pregnancy and breastfeeding**: Dexrazoxane for Injection can harm your unborn baby.
    - Avoid getting pregnant while on Dexrazoxane for Injection. Use effective birth control.
    - Tell your healthcare professional right away if you think you are pregnant while on Dexrazoxane for Injection.
    - If you are pregnant or plan to become pregnant, there are specific risks you should discuss with your healthcare professional.
    - It is not known if Dexrazoxane for Injection passes into your breast milk. You should not breast feed your baby if you are being treated with Dexrazoxane for Injection.
- **Liver and Kidney problems:** Your healthcare professional will adjust your dose of Dexrazoxane for Injection if you have liver or kidney problems. Your blood cells and liver and kidney function will need to be tested often.

What is Dexrazoxane for Injection used for?

Dexrazoxane for Injection is used in adults to reduce or prevent heart damage caused by:

- Treatment with doxorubicin in women with breast cancer that has spread to other parts of the body.

Dexrazoxane for Injection is not an anticancer drug.

How does Dexrazoxane for Injection work?

Dexrazoxane for Injection enters cell membranes to protect the heart muscle from heart damage caused by other anti- cancer medicines.

What are the ingredients in Dexrazoxane for Injection ?

Medicinal ingredient: Dexrazoxane

Non-medicinal ingredient: Hydrochloric acid

Dexrazoxane for Injection comes in the following dosage forms:

Dexrazoxane for Injection is a lyophilized powder for injection. It is available in vials of 250 mg.

Do not use Dexrazoxane for Injection if:

- you are allergic to dexrazoxane, any other ingredients of Dexrazoxane for Injection , or components of the container.
- you are under 18 years of age.
- your cancer treatment does not include doxorubicin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Dexrazoxane for Injection. Talk about any health conditions or problems you may have, including if you:

- Have liver problems
- Have kidney problems
- Have heart problems
- Are 65 years of age or older
- Are pregnant, think you are pregnant or plan to become pregnant
- Are breastfeeding

Other warnings you should know about:

Dexrazoxane for Injection may increase the risk of having:

- Cancer of the blood **(Acute Myeloid Leukaemia)**
- Blood clots in the vein or artery **(thromboembolism)**

See the "**Serious side effects and what to do about them**" table, below, for more information on these and other serious side effects.

Check-ups and Testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will do:

- Blood and urine tests to check your liver, kidney and blood health
- Imaging tests to check your heart health

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Dexrazoxane for Injection:

- Medicines used to treat different cancers such as fluorouracil and cyclophosphamide.

How to take Dexrazoxane for Injection:

- Your healthcare professional will mix Dexrazoxane for Injection into a solution. They will inject the solution into a vein by rapid intravenous infusion. You will receive this injection in a clinic or hospital setting.
- Dexrazoxane for Injection is given to you between 15 to 30 minutes before the treatment

with an anti-cancer drug called doxorubicin.

- Your healthcare professional will follow proper safe handling directions. Gloves should be worn.

Usual dose:

- **Adults:** Your healthcare professional will choose the dose of Dexrazoxane for Injection that is right for you.

Your healthcare professional may interrupt or stop your treatment or reduce your dose. This may happen if you:

- experience side effects, or
- your disease has gotten worse.

Overdose:

If you think you, or a person you are caring for, have taken too much Dexrazoxane for Injection, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Dexrazoxane for Injection ?

These are not all the possible side effects you may have when taking Dexrazoxane for Injection. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- hair loss
- nausea, vomiting, diarrhea
- tiredness
- mouth sores
- fever, infection
- redness of the blood vessels
- difficulty swallowing, burning sensation of the esophagus
- itching
- bleeding
- tissue swelling, redness and pain at the injection site
- skin reaction in areas where other agents were used

Dexrazoxane for Injection might cause abnormal blood test results. Your healthcare professional will treat you accordingly.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Myelosuppression (a large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising,		√	
chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection			
Neurotoxicity (damage to the nervous system): agitation, blurred vision, confusion, convulsions, difficulty speaking, dizziness, hallucinations, headache, impaired thinking, loss of control of body movements, memory loss, mental status changes, nervousness, numbness and tingling, vision loss, muscle weakness, seizures		√	
COMMON			
Congestive Heart Failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		√	
Phlebitis (swelling of a vein): pain, tenderness, redness or swelling		√	
Myelodysplastic Syndrome or Acute Myeloid Leukaemia (a group of diseases in which the body produces large numbers of abnormal blood cells): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool		√	
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, loss of consciousness, swelling of the face, lips, tongue or throat.		√	
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin		√	
that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Your healthcare professional will store, handle and dispose of Dexrazoxane for Injection.

- **Dry powder:** Store vials at 15-25°C.
- **Reconstituted solution:** Store 30 minutes at room temperature or a maximum of 3 hours at 2-8°C.
- **Reconstituted and diluted solution:** Store 1 hour at room temperature or a maximum of 4 hours at 2-8°C.

Keep out of reach and sight of children.

If you want more information about Dexrazoxane for Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://www.hikma.com, or by calling 1-800-656-0793.

This leaflet was prepared by Hikma Canada Ltd.

Last Revised MAY 23, 2025