DRUG NAME: Dexrazoxane

SYNONYM(S): ICRF-187, (+)-1,2-Di(3,5-dioxopiperazin-1-yl)propane[1]

COMMON TRADE NAME(S): ZINECARD®, CARDIOXANE®

CLASSIFICATION: Cytoprotectant

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Dexrazoxane is a cyclic derivative of edetic acid (EDTA) that readily penetrates cell membranes. Dexrazoxane is converted intracellularly to a ring-opened chelating agent. The hydrolysis products of dexrazoxane are thought to exert their effects by chelating free or bound intracellular iron in the myocardium, thus preventing the formation of the anthracycline-iron complex and resultant free radical generation.[2,3] The hydrolysis products are believed to be responsible for most of the activity of dexrazoxane.[4]

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	highest concentrations found in the liver and kidneys	
	cross blood brain barrier?	no
	volume of distribution	29-90 L
	plasma protein binding	< 2%
Metabolism	hydrolyzed by dihydropyrimidine aminohydrolase (DHPase) in the liver and kidney, and dihydroorotase (DHOase) in the heart, liver, kidney, erythrocytes and leukocytes	
	active metabolite(s)	yes
	inactive metabolite(s)	no information found
Excretion	predominantly renal (unchanged)	
	urine	42-48%
	feces	no information found
	terminal half life	2-4 h
	clearance	13.8 L/h (0.29 L/h/kg)
Gender	clearance: not clinically significant	
Elderly	no information found	
Children	volume of distribution: 0.96 L/kg clearance: 0.36 L/h/kg	
Ethnicity	no information found	

Adapted from standard references[4,5] unless specified otherwise.

Developed: 1 September 2005
Revised: 1 September 2025

USES:

Primary uses:

*Cardioprotectant against doxorubicin-induced cardiotoxicity

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- should not be used as a chemotherapeutic agent[6]
- should only be used in chemotherapy regimens containing doxorubicin[6]

Carcinogenicity: Secondary malignancies (acute myeloid leukemia, T-cell lymphoma, B-cell lymphoma, cutaneous basal cell or squamous cell carcinoma) have been reported in patients treated chronically with oral razoxane, a racemic mixture containing dexrazoxane as the S(+)-enantiomer. Secondary acute myeloid leukemia/myelodysplastic syndrome have been observed in patients receiving dexrazoxane in combination with chemotherapy.[6]

Mutagenicity: Not mutagenic in Ames test. Dexrazoxane is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[7,8]

Fertility: Animal studies have shown impaired fertility at maturity in both males and females at a dose of 8 mg/kg.[7] There is no conclusive evidence about the adverse effect of dexrazoxane on human fertility.[6]

Pregnancy: In animal studies, embryotoxicity and teratogenicity were observed when dexrazoxane was administered during organogenesis at doses significantly lower than clinically recommended doses. Teratogenic effects included imperforate anus, microphthalmia, anophthalmia, and agenesis of the gallbladder and intermediate lobe of the lung.[6]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2,7]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

Determination of the effect of dexrazoxane alone on patient tolerability is difficult given the morbidity in this patient population and the effect of concurrently administered anthracyclines and other chemotherapeutic agents. The only adverse event that was observed in 5% more patients on FAC + dexrazoxane than on FAC + placebo was pain on injection.[3]

ORGAN SITE	SIDE EFFECT
blood/bone marrow/ febrile neutropenia	granulocytopenia (severe 88%)*
	thrombocytopenia (severe 10%)*
cardiovascular (general)	congestive heart failure (1%)*
	phlebitis (5%)*
constitutional symptoms	fatigue/malaise (62%)*

Developed: 1 September 2005
Revised: 1 September 2025

ORGAN SITE	SIDE EFFECT
	fever (35%)*
dermatology/skin	*extravasation hazard: none*
	alopecia (94%)*
	erythema/streaking (7%)*
	recall skin reaction (1%)*
	urticaria (4%)*
gastrointestinal	*emetogenic potential: high moderate**
	anorexia (50%)*
	diarrhea (22%)*
	dysphagia (6%)*
	esophagitis (5%)*
	nausea (82%)*
	stomatitis (36%)*
	vomiting (63%)*
hemorrhage	hemorrhage (2%)*
infection	infection and/or sepsis (31%)*
neoplasms	secondary acute myeloid leukemia/myelodysplastic syndrome[6]
neurology	neurotoxicity (16%)*
pain	***pain on injection (11%)***

Adapted from standard reference[2] unless specified otherwise.

***Adverse events and incidences were those reported for dexrazoxane when given with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC regimen) and likely attributable to the FAC regimen itself.**

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dexrazoxane + combination of 5-FU, doxorubicin and cyclophosphamide	may experience more severe leucopenia, granulocytopenia and thrombocytopenia at nadir, but no significant effect on recovery time[7]	unknown	none (clinically non-significant)[9]

SUPPLY AND STORAGE:

***Injection*:**

Juno Pharmaceuticals Corp. supplies dexrazoxane as 250 mg and 500 mg single-dose (preservative free) vials of lyophilized powder. Store at room temperature.[10]

Developed: 1 September 2005
Revised: 1 September 2025

Pfizer Canada Inc. supplies dexrazoxane as 250 mg and 500 mg single-dose (preservative free) vials of lyophilized powder. Store at room temperature.[6]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

Additional information: Reconstituted solution must be further diluted for administration.[11]

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[11]
Intermittent infusion	***over 15 min***[6]***;*** longer infusions (e.g., 30 min) have been used[1] • administer doxorubicin within 30 minutes of the completion of dexrazoxane infusion[6]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: with each dose of doxorubicin	recommended dosage ratio of dexrazoxane:doxorubicin is 10:1 (e.g., dexrazoxane 500 mg/m^2: doxorubicin 50mg/m^2) IV for one dose[12]
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	

Developed: 1 September 2005
Revised: 1 September 2025

Dosage in renal failure:	CrCl <40 mL/min: reduce dose by 50%[6]; recommended dosage ratio[6] of dexrazoxane:doxorubicin is 5:1

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:	reduce dexrazoxane proportionate to doxorubicin dose reduction in order to maintain the recommended 10:1 dosage ratio of dexrazoxane: doxorubicin[6]
Dosage in dialysis	possibly dialyzable[2,8]

Children:

Intravenous:	10:1 ratio of dexrazoxane: doxorubicin IV prior to each dose of doxorubicin[13,14]

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