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A DRUG NAME: DEXRAZOXANE

SYNONYM(S): 2,6-Piperazinedione

COMMON TRADE NAME(S): Zinecard® (Pfizer Canada)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Dexrazoxane, a cyclic derivative of EDTA, appears to protect the myocardium from anthracycline induced cardiotoxicity. The mechanism of action is not clearly defined. The hydrolysis products of dexrazoxane have been shown to chelate both free and bound intracellular iron, including iron that is bound in anthracycline complexes, thereby preventing the generation of cardiotoxic reactive oxygen species. Dexrazoxane appears to potentiate the myelotoxicity of co-administered cytotoxic agents, and may lead to reduced efficacy, possibly because of lower dose intensity.

Oral Absorption	No
Distribution	Dexrazoxane is rapidly distributed into body's tissues and fluids, the highest concentration being found in the hepatic and renal tissues. The disposition kinetics of dexrazoxane are dose independent, demonstrating a linear relationship between the area under the plasma concentration-time curve and doses. Dexrazoxane does not appear to alter the pharmacokinetics of doxorubicin.
	Cross blood brain barrier? No
	PPB Not bound
Metabolism	Dexrazoxane is hydrolysed by the enzyme dihydropyrimidine amidohydrolase in the liver and kidney to active metabolites that are capable of binding to metal ions.
	Active metabolite(s) Yes
	Inactive metabolite(s) No
Excretion	Dexrazoxane is predominantly eliminated in the urine.
	t _{1/2} 2 to 4 hours

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C INDICATIONS AND STATUS

* For reducing (preventing) the incidence and severity of cardiotoxicity associated with doxorubicin administration for the treatment of breast cancer in patients who have already experienced a partial response or at least maintain stable disease. It should be only used with chemotherapy regimens containing doxorubicin and in patients where tolerance to a full dose of doxorubicin has been established.

* Health Canada approved indication

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D ADVERSE EFFECTS (Incidence > placebo group)

ORGAN SITE	SIDE EFFECT*	ONSET**
Dermatologic and Hypersensitivity	Urticaria (2% ↑)	I
	Pain on injection (7% ↑)	I
Extravasation hazard (refer to Appendix 2)	None	
Generalized	Infection (3% ↑)	E
	Fever (2% ↑)	E
Hematologic	Grade 3 / 4 neutropenia (3% ↑)	E
	Grade 3 / 4 thrombocytopenia (1% ↑)	E
Nervous system	Neurotoxicity (3% ↑)	D

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days)

E = early (days to weeks)

D = delayed (weeks to months)

L = late (months to years)

Clinical trial data for adverse effects were collected from patients receiving anthracycline-based therapy for advanced breast cancer. Only adverse effects which occurred with a higher incidence in patients receiving dexrazoxane are presented.

There was a slightly higher incidence of myelosuppression, infection and fever in patients who received dexrazoxane, and the early drop out rate was also higher in these patients. Of the non-hematological adverse events, only **pain on injection** was the most frequent in patients treated with dexrazoxane versus placebo, but this was generally mild to moderate.

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E DOSING

Refer to protocol by which patient is being treated. Use only in patients who have received a cumulative doxorubicin dose of 300 mg/m², who are continuing with doxorubicin and have responding or stable disease. Dexrazoxane 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 2 consecutive courses.

Adults:

IV: 500mg/m², 30 minutes before to 15 minutes after the start of doxorubicin administration.
(i.e. Dexrazoxane: doxorubicin dose in 10:1 ratio)

Dosage with myelosuppression: Dexrazoxane may potentiate hematological toxicity induced by chemotherapy or radiation. Refer to the [Doxorubicin](#) monograph for doxorubicin dose modification recommendations.

Dosage with renal impairment: As most of an administered dose is eliminated via the kidneys, caution is advised in patients with renal impairment. Refer to the [Doxorubicin](#) monograph for doxorubicin dose modification recommendations.

Creatinine clearance (mL/min)	Dexrazoxane (% of previous dose)
< 40	50% (i.e. 250mg/m ²)

Dosage with hepatic impairment: The pharmacokinetics of dexrazoxane have not been determined in patients with hepatic impairment. As doxorubicin doses should be reduced in hyperbilirubinemia, a reduction of dexrazoxane to maintain a ratio of 10:1 with doxorubicin can be considered

Dosage in the elderly: No specific recommendations found; use with caution as elderly patients have a greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or drug therapy which may exacerbate toxicity

Children: Safety and efficacy have not been established.

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F ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

- Use standard cytotoxic handling and preparation procedures for dexrazoxane
- Should be reconstituted with the diluent provided, Sodium Lactate.
- Should be given within 30 minutes before anthracycline administration.
- May be given undiluted as an IV bolus or as a rapid IV drip infusion (from an empty viaflex bag); infused over 15 minutes.
- Do not admix with other drugs.
- The diluted solution is only stable for 6 hours under refrigeration.

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G SPECIAL PRECAUTIONS

Dexrazoxane should not be used as a chemotherapeutic agent. Dexrazoxane may reduce the efficacy and potentiate myelosuppression (and infection) associated with cytotoxic chemotherapy; patients should be monitored closely. Dexrazoxane should not be used in place of scheduled dose reductions for hematologic and non-cardiac toxicity. The use of dexrazoxane does not eliminate the potential for anthracycline induced cardiac toxicity; therefore, monitor cardiac function carefully

Secondary malignancies (AML, lymphoma, cutaneous carcinomas) have been reported in patients treated with razoxane (dexrazoxane is the S-enantiomer). Although dexrazoxane is not mutagenic, it is **clastogenic, teratogenic** and **embryotoxic** in animal models and should not be used in **pregnancy**. Adequate contraception should be used by both sexes, during dexrazoxane and anthracycline treatment, and at for at least 6 months after cessation. Dexrazoxane did not change the mutagenic or genotoxic properties of doxorubicin. There is no conclusive information about dexrazoxane adversely affecting human **fertility**. **Breast feeding** is not recommended due to the potential secretion into breast milk.

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H INTERACTIONS

Based on a kinetic study, dexrazoxane does not appear to influence the pharmacokinetics of doxorubicin. Since dexrazoxane may produce mild myelosuppressive effects, additive effects may occur with the use of other chemotherapeutic agents.

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I RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring**

- Regular clinical assessment for chemotherapy toxicity and cardiotoxicity. Grade toxicity using the current [NCI Common Toxicity Criteria Version](#)
- Baseline and regular renal and hepatic function tests
- Baseline and regular CBC

Suggested Clinical Monitoring

Refer to [Doxorubicin](#) monograph for recommendations regarding cardiac monitoring.

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REFERENCES

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