

Drug Monograph

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A - Drug Name

dexrazoxane

COMMON TRADE NAME(S): Zinecard®

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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. It should not be used with FAC chemotherapy.

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 metabolites	yes
	Inactive metabolites	no
Elimination	Dexrazoxane is predominantly eliminated in the urine.	
	Half-life	2 to 4 hours

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C - Indications and Status

Health Canada Approvals:

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. It should be only used with chemotherapy regimens containing doxorubicin, after a cumulative dose of 300mg/m², and in patients where tolerance to a full dose of doxorubicin has been established.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains adverse effects where incidence in the dexrazoxane+chemotherapy group is greater than the placebo+chemotherapy group.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Urticaria (2% ↑)	I
Hematological	Myelosuppression ± infection, bleeding (grade 3 or 4: 3% ↑)	E
Injection site	Injection site reaction (pain on injection: 7% ↑)	I
Neoplastic	Secondary malignancy	D
Nervous System	Neurotoxicity (3% ↑)	D

* "Incidence" may refer to an absolute value or the higher value from a reported range.
"Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** 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
- Avoid use with FAC.
- 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.
- Do not delay initiation beyond cycle 7.

Adults:

IV: : Dexrazoxane: doxorubicin dose in a ratio of 10:1 (i.e. 500mg/m² dexrazoxane: 50mg/m² doxorubicin) IV infusion over 15 minutes before the administration of doxorubicin. Administer doxorubicin within 30 minutes after the completion of dexrazoxane. Dose should not exceed 500mg/m²

Dosage with Toxicity:

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

modification recommendations.

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/↑ LFTs, a reduction of dexrazoxane to maintain a ratio of 10:1 with doxorubicin should be considered.

Dosage with Renal Impairment:

As most of an administered dose is eliminated via the kidneys, caution is advised in patients with renal impairment. Likely to be removed by dialysis. Refer to the [doxorubicin](#) drug monograph for doxorubicin dose modification recommendations.

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

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:

Not indicated for patients <18 years old due to an increased risk of second primary malignancy. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) have been reported.

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F - Administration Guidelines

- Use standard cytotoxic handling and preparation procedures for dexrazoxane
- Should be reconstituted with Sterile Water for Injection, USP; This must be further diluted with Lactated Ringer's Injection, USP to a concentration between 1.3 to 3 mg/mL. Note: Diluent is no longer provided with the package.*
- Should be given over 15 minutes before the administration of doxorubicin. Administer doxorubicin within 30 minutes after the completion of dexrazoxane. Do not give as an IV push.
- Do not admix with other drugs.
- See the dexrazoxane product monograph for detailed storage and stability information.

* During the temporary drug shortage, other brands may become available; the reconstitution and dilution instructions of the imported US-labelled dexrazoxane are different from the Canadian product. Refer to the US-labelled product information for instructions on this product. ([Health Canada](#), Dec 2020)

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Use with FAC should be avoided
- Dexrazoxane should not be used as a chemotherapeutic agent
- Do not use with non-anthracycline chemotherapy regimens

Other Warnings/Precautions:

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

Other Drug Properties:

- Carcinogenicity: Secondary malignancies (AML, lymphoma, cutaneous carcinomas) have been reported in patients treated with razoxane (dexrazoxane is the S-enantiomer). Dexrazoxane did not change the mutagenic or genotoxic properties of doxorubicin.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Teratogenicity: Yes
- Embryotoxicity: Yes
Dexrazoxane is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (general recommendation).
- Breastfeeding: Not recommended
- Fertility effects: Unknown

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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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Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and prior to each dose
Liver function tests	Baseline and prior to each dose
Renal function tests	Baseline and prior to each dose
Clinical assessment for chemotherapy toxicity and cardiotoxicity	Prior to each dose

Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Refer to doxorubicin drug monograph for recommendations regarding cardiac monitoring.	

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K - References

Dexrazoxane Hydrochloride: AHFS Drug Information (Online). Accessed on March 6, 2012.

Health Canada Safety Alert: Importation of US-labelled Dexrazoxane for Injection distributed by Mylan Pharmaceuticals ULC due to shortage of Canadian-labelled Dexrazoxane, December 1, 2020.

Product Monograph: Zinecard® (Dexrazoxane). Pfizer Canada Inc., March 30, 2015.

Wiseman LR, Spencer CM. Dexrazoxane: A review of its use as a cardioprotective agent in patients receiving anthracycline-base chemotherapy. *Drugs* 1998;56(3):385-403.

December 2020 Noted different preparation procedure of US-labelled product during drug shortage (Health Canada safety alert)

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L - Disclaimer

Refer to the [New Drug Funding Program](#) or [Ontario Public Drug Programs](#) websites for the most up-to-date public funding information.

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