

Dexrazoxane use for anthracycline cardiotoxicity prevention

1. What is dexrazoxane and what it is used for?

At BC Cancer dexrazoxane is primarily used as a cardioprotective agent to reduce doxorubicin-induced cardiotoxicity. It can also be used with other anthracyclines.

Dexrazoxane is a derivative of ethylenediaminetetraacetic acid (EDTA) and is thought to protect cardiac tissue by mitigating both the oxidative stress and topoisomerase II β -mediated DNA damage induced by doxorubicin. Dexrazoxane chelates iron which reduces the number of metal ions available to complex with anthracyclines. This limits the formation of the reactive oxygen species thought to be associated with anthracycline-induced cardiotoxicity.¹ In addition, dexrazoxane acts intracellularly in cardiac cells to inhibit the enzyme topoisomerase II β , which, when bound by doxorubicin, can induce myocyte DNA damage and cardiotoxicity.

Dexrazoxane can be used in conjunction with doxorubicin (or other anthracyclines) in patients who have reached a cumulative doxorubicin dose of 300 mg/m² (or equivalent) but who may still benefit from continued therapy. For information on anthracycline dose thresholds see the Pharmacy FAQ [Lifetime Cumulative Dose Documentation for Anthracyclines and Bleomycin](#). The use of dexrazoxane does not eliminate the risk of cardiotoxicity from anthracycline use. Therefore, cardiac function tests, such as Left Ventricular Ejection Fraction (LVEF), should be used to assess appropriateness of continued therapy.

Dose adjustments for dexrazoxane are required in renal and hepatic impairment. See the BC Cancer Drug Manual product [monograph](#) for more information on dosing.

Dexrazoxane can also be used to treat anthracycline extravasation; however, BC Cancer currently does not use dexrazoxane for this purpose as outlined in Policy III-20 Prevention and Management of Extravasation of Chemotherapy.

NOTE: a CAP approval is required for reimbursement in the adult cancer setting.

2. How is dexrazoxane prepared?

Refer to the product monograph for the specific brand and formulation of dexrazoxane in question.

The preparation of the Zinecard® brand of dexrazoxane is described here as an example. It involves both reconstitution and further dilution as described below:²

- Reconstitute vial with *Sterile Water for Injection, USP*
 - The concentration of the reconstituted solution is 10 mg/mL
 - Reconstituted vials are stable for 30 minutes at room temperature or up to 3 hours under refrigeration
- Add the required volume of the reconstituted solution to an empty viaflex bag
- Further dilute the reconstituted solution with *Lactated Ringers Injection, USP*, to a final concentration range of 1.3 – 3 mg/mL
 - The final product is stable for 1 hour at room temperature or up to 4 hours under refrigeration

3. In what sequence should the drugs be given?

Dexrazoxane is administered via intravenous infusion *first*. Doxorubicin should be administered *within 30 minutes* of the completion of the dexrazoxane infusion *as dexrazoxane has a short plasma half-life*.³

4. The product monograph indicates that dexrazoxane should be infused over 15 minutes, but the prescribed dose for my patient will run longer than 15 minutes. Is this acceptable?

Although most manufacturers recommend infusing dexrazoxane over 15 minutes², longer infusion times have been used.³ Due to newer IV pump programming limits which cap infusion rates at 999 mL/hr, and the need to maintain dexrazoxane within a specified concentration range, larger doses of dexrazoxane may not be deliverable within the recommended 15-minute infusion timeframe. In these circumstances, BC Cancer best practice has been to administer dexrazoxane via intravenous infusion over **15 – 30 minutes**.

5. It seems as though the ZINECARD® brand of dexrazoxane is also stable in NS – can NS be substituted for Lactated Ringer’s Injection for further dilution of the reconstituted solution?

Dexrazoxane (ZINECARD®) is stable in NS, however this was only recommended when it was reconstituted with 0.167M sodium lactate injection, the previously supplied diluent in ZINECARD® packages.⁵ The updated ZINECARD® product monograph recommends a new reconstitution and dilution procedure to control final product pH and thus tolerability. It very clearly states that now *only* Sterile Water for Injection, USP, should be used for reconstitution.² Therefore, when using the current ZINECARD® (Pfizer) brand, only Lactated Ringer’s Injection, USP, should be used as the final dilution solution to prepare the intravenous infusion bag.

Refer to your institutional standards for flushing the line during administration. It is our practice to flush the line with the infusion solution (Lactated Ringer’s) if no other diluent choices are specified in the drug monograph or treatment protocol.

6. There has been a shortage of dexrazoxane (ZINECARD®) and a US-labelled brand is available. What should we know about preparation procedures of this brand?

During temporary dexrazoxane drug shortages, other brands may become available that are imported from [outside Canada](#). The reconstitution and dilution instructions of these brands may be different from the Canadian product. Refer to the US-labelled product information for instructions on the particular product.⁶ The [Chemotherapy Preparation and Stability Chart](#) in the [BC Cancer Drug Manual](#) also lists different manufacturers and their preparation procedures [for the products currently in use here](#).⁷

7. The dexrazoxane for injection (ZINECARD®) product monograph has a boxed warning that says it “should not be administered in a dose that exceeds 500 mg/m². However, the BC Cancer treatment protocol prescribes doxorubicin 60 mg/m², which at the recommended 10:1 ratio would require a dexrazoxane dose of 600 mg/m². Given this discrepancy, what is the maximum allowable dose of dexrazoxane?

Pfizer Canada’s ZINECARD® product monograph lists a 500 mg/m² dose cap as a boxed warning. However, the product monograph’s Clinical Pharmacology section mentions

pharmacokinetic studies in cancer patients using doses ranging up to 900 mg/m² with 60 mg/m² of doxorubicin, and the Overdosage section mentions a maximum dose administered during cardioprotection trials of 1000 mg/m² every three weeks. Other sources, including the Pfizer US product monograph, do not list the 500 mg/m² dose cap. BC Cancer does not consider the 500 mg/m² a true clinical dose limit for dexrazoxane.

When administered as a single agent, dexrazoxane side effects can include myelosuppression (neutropenia), nausea, vomiting, mucositis, alopecia, transient increases in liver enzymes, increased urinary excretion of iron and zinc, and local injection site reactions.^{3,8} Refer to the product monograph.

References:

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4. IBM Micromedex[®] IV Compatibility (database on the internet). Dexrazoxane. Powered by Trissel's[™] 2 Clinical Pharmaceutics Database (Parenteral Compatibility). Available at: www.micromedexsolutions.com. Accessed 28 October 2019.
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6. Health Canada. Recalls and Safety Alerts: Importation of US-labelled Dexrazoxane for Injection distributed by Mylan Pharmaceuticals ULC due to shortage of Canadian-labelled Dexrazoxane. Ottawa, Ontario: 1 December 2020.
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8. Langer SW. Dexrazoxane for the treatment of chemotherapy-related side effects. *Cancer Manag Res*. 2014;6:357-363. Published 2014 Sep 15. doi:10.2147/CMAR.S47238