

## PRODUCT MONOGRAPH

<sup>Pr</sup>**ZINECARD**<sup>®</sup>

Dexrazoxane for injection

250 mg & 500 mg vials, 10 mg/mL

Sterile

Cardioprotective Agent

Pfizer Canada Inc.  
17,300 Trans-Canada Highway  
Kirkland, Quebec H9J 2M5

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# Pr ZINECARD®

Dexrazoxane for injection

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	<b>Dosage form</b> <u>Lyophilized powder</u> 250 mg and 500 mg single dose vials  <b>Nominal concentration</b> 10 mg/mL  <b>Strength</b> 250 mg/25 mL and 500 mg/50 mL	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

ZINECARD (dexrazoxane) 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.

ZINECARD 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. ZINECARD should be used only after tolerance to a full dose doxorubicin has been established (see WARNINGS AND PRECAUTIONS).

**Geriatrics (≥ 65 years of age):** Clinical studies of ZINECARD did not include sufficient numbers of subjects 65 and over to determine whether they respond differently from younger subjects (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

**Pediatrics (< 18 years of age):** ZINECARD is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

## CONTRAINDICATIONS

- ZINECARD (dexrazoxane) should not be used as a chemotherapeutic agent.
- ZINECARD 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 DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Do not use ZINECARD with non-anthracycline chemotherapy regimens.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

**ZINECARD (dexrazoxane) is a potent drug and should be used only by physicians experienced with cancer chemotherapy drugs.**

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

## **General**

ZINECARD should only be used in those patients who have received a cumulative doxorubicin dose of 300 mg/m<sup>2</sup> and are continuing with doxorubicin therapy.

ZINECARD should be administered only after the tolerance of the patient to the full dose of doxorubicin-containing chemotherapeutic regimen has been determined. ZINECARD 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 ZINECARD after 6 courses of chemotherapy. ZINECARD 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 ZINECARD administration. Therefore, the administration of ZINECARD 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. ZINECARD is not indicated for use in patients below the age of 18 years.

## **Cardiovascular**

Although clinical studies have shown that patients receiving FAC with ZINECARD may receive a higher cumulative dose of doxorubicin before experiencing cardiac toxicity than patients receiving FAC without ZINECARD, the use of ZINECARD in patients who have already received a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup> without ZINECARD, does not eliminate the potential for anthracycline induced cardiac toxicity. Therefore, cardiac function should be carefully monitored.

## **Hematologic**

ZINECARD may **add to** the myelosuppression caused by chemotherapeutic agents. ZINECARD 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 ZINECARD have not been evaluated in patients with hepatic impairment. The ZINECARD dose is dependent upon the dose of doxorubicin. Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

### **Immune**

In controlled studies, a slightly higher incidence of infection associated with granulocytopenia occurred in patients receiving ZINECARD. As ZINECARD will always be used with cytotoxic drugs, patients should be monitored closely. While the myelosuppressive effects of ZINECARD at the recommended dose are considered to be mild, additive effects upon the myelosuppressive activity of chemotherapeutic agents may occur.

### **Renal**

Patients with moderate or severe renal insufficiency: Greater exposure to dexrazoxane may occur in patients with compromised renal function. The ZINECARD dose should be reduced by 50% in patients with creatinine clearance values <40 mL/min (see DOSAGE AND ADMINISTRATION).

### **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.

### **Sexual Function/Reproduction**

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

### **Special Populations**

**Pregnant Women:** ZINECARD 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 PHARMACEUTICAL INFORMATION, Toxicology).

ZINECARD 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.

**Nursing Women:** Mothers should be advised not to breastfeed while undergoing therapy with ZINECARD.

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**.

**Pediatrics (< 18 years of age):** ZINECARD 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).

**Geriatrics ( $\geq 65$  years of age):** Clinical studies of ZINECARD 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.

### **Monitoring and Laboratory Tests**

- As ZINECARD 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 WARNINGS AND PRECAUTIONS, Hematologic; Immune and ADVERSE REACTIONS).
- Patients should be monitored for cardiac function before and periodically during therapy to assess left ventricular ejection fraction (LVEF) (see 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 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 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 WARNINGS AND PRECAUTIONS, Renal and DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

ZINECARD (dexrazoxane) at a dose of 500 mg/m<sup>2</sup> 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<sup>2</sup> in each of the trials. Courses were repeated every three weeks provided recovery from toxicity had occurred. Table 1 lists the incidence of clinical adverse experiences for patients receiving either ZINECARD or placebo in the breast cancer studies.

<b>Table 1 – PERCENTAGE OF BREAST CANCER PATIENTS WITH ADVERSE EXPERIENCE</b>		
<b>ADVERSE EXPERIENCE</b>	<b><u>FAC + ZINECARD</u></b> N = 244 (%)	<b><u>FAC + PLACEBO</u></b> 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
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 + ZINECARD than on FAC + placebo was pain on injection. However, the early drop-out rate for patients receiving Zinecard was higher than for patients receiving placebo.

**Myelosuppression:** Eighty-eight percent (88%) of breast cancer patients receiving FAC + 500 mg/m<sup>2</sup> ZINECARD and 85% of patients receiving FAC + placebo experienced Grade 3 or 4 granulocytopenia. Ten percent (10%) of patients receiving FAC + ZINECARD 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 + ZINECARD or FAC + placebo.

**Hepatic and Renal: Very few patients receiving FAC + ZINECARD 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.**

## **DRUG INTERACTIONS**

### **Overview**

Based on a kinetic study, ZINECARD (dexrazoxane) does not appear to influence the pharmacokinetics of doxorubicin.

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

### **Drug-Drug Interaction**

Interactions with other drugs have not been established.

### **Drug-Food Interaction**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal product have not been established.

### **Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

ZINECARD (dexrazoxane) should be reconstituted with Sterile Water for Injection, USP to a concentration of 10 mg/mL. The reconstituted Zinecard 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 the DOSAGE AND ADMINISTRATION, Reconstitution section.

### Recommended Dose and Dosage Adjustment

The recommended dosage ratio of ZINECARD: doxorubicin is 10:1 (e.g. 500 mg/m<sup>2</sup> ZINECARD: 50mg/m<sup>2</sup> doxorubicin) (see WARNINGS AND PRECAUTIONS).

**Hepatic insufficiency:** Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD 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 ZINECARD:doxorubicin is 5:1 (e.g. 250 mg/m<sup>2</sup> ZINECARD:50 mg/m<sup>2</sup> doxorubicin). Creatinine clearance can be determined from a 24-hour urinary creatinine collection or estimated using the Cockcroft-Gault equation (assuming stable renal function):

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

### Administration:

- The reconstituted solution when further diluted with Lactated Ringer's Injection MUST be given by rapid drip intravenous infusion. DO NOT ADMINISTER VIA IV PUSH. Administer the final diluted solution of ZINECARD over 15 minutes before the administration of doxorubicin. Administer doxorubicin within 30 minutes after the completion of ZINECARD infusion.
- ZINECARD should be administered only after the tolerance of the patient to the full dose of doxorubicin-containing chemotherapeutic regimen has been determined.
- ZINECARD 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.
- ZINECARD should be given only to patients who have already experienced partial response or at least maintained stable disease.

**Reconstitution:**

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

The reconstituted ZINECARD solution is intended for further dilution for rapid intravenous drip infusion. DO NOT ADMINISTER VIA IV PUSH.

**Reconstitution table**

Vial Size	Sterile Water for Injection (SWFI) Diluent Added to Vial (mL)	Approximate Available Volume (mL)	Nominal Concentration (mg/mL)
250 mg	25	25*	10
500 mg	50	50*	10

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

Reconstitute each vial with Sterile Water for Injection, USP, according to the above table. The reconstituted ZINECARD 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 STORAGE AND STABILITY).

**Dilution following reconstitution:** The resultant reconstituted ZINECARD 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 STORAGE AND STABILITY).

**Storage:**

See STORAGE AND STABILITY, when reconstituted and further diluted for use.

**Incompatibility:**

Unless specific compatibility data are available, ZINECARD should not be mixed with other drugs.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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<sup>2</sup> every three weeks.

Disposition studies with ZINECARD (dexrazoxane) 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.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

ZINECARD (dexrazoxane) is a cyclic derivative of EDTA which, unlike EDTA, readily penetrates cell membranes. ZINECARD was shown to be able to protect the myocardium from anthracycline-induced cardiotoxicity. The mechanism by which ZINECARD 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.

### Pharmacokinetics

Pharmacokinetic studies have been performed in advanced cancer patients with normal renal and hepatic function following administration of ZINECARD as a 15 minute I.V. infusion over a dose-range of 60 to 900 mg/m<sup>2</sup> with 60 mg/m<sup>2</sup> of doxorubicin, and at a fixed dose of 500 mg/m<sup>2</sup> with 50 mg/m<sup>2</sup> doxorubicin.

**Absorption:** The mean peak plasma concentration of dexrazoxane at the end of the 15 minute infusion was 36.5 µg/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 ( $t_{1/2, \lambda_1}$ : ~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<sup>2</sup>, respectively. This suggests minimal tissue uptake of dexrazoxane and its confinement in a volume equal to the total body water (25 L/m<sup>2</sup>).

*In vitro* studies have shown that ZINECARD is not bound to plasma proteins.

**Metabolism:** Plasma clearance of ZINECARD is via both renal and nonrenal elimination. The nonrenal component is mainly metabolic. Qualitative metabolism studies with ZINECARD 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.

**Excretion:** The means ( $\pm$  *sd*; *range*) of the terminal elimination half-life ( $t_{1/2, \lambda_z}$ ) and systemic clearance ( $CL_s$ ) were 2.5 ( $\pm$  0.4; 1.8 to 3.3) hours and 9.56 ( $\pm$  3.56; 5.93 to 16.71) L/Hr/m<sup>2</sup>, 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  $CL_s$ ,  $t_{1/2}$ , and  $V_{ss}$  indicate that its disposition kinetics are apparently dose-independent. The mean ( $\pm$  *sd*; *range*) urinary excretion (expressed as percent dose) for dexrazoxane was 37.0% ( $\pm$  15.0; 17.1 to 61.2%).

### ***Special Populations and Conditions***

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

### **STORAGE AND STABILITY**

#### Unreconstituted Vials

ZINECARD (dexrazoxane) lyophilized powder for injection should be stored at controlled room temperature, 15 -30°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 DOSAGE AND ADMINISTRATION, 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 DOSAGE AND ADMINISTRATION, Reconstitution).

### **SPECIAL HANDLING INSTRUCTIONS**

Caution in the handling and preparation of the reconstituted solution must be exercised and the use of gloves is recommended. If ZINECARD (dexrazoxane) 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 ZINECARD. 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.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

ZINECARD (dexrazoxane) is available in:

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

500 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, NF.

The 500 mg vial contains 500 mg of dexrazoxane; pH is adjusted with hydrochloric acid, NF.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

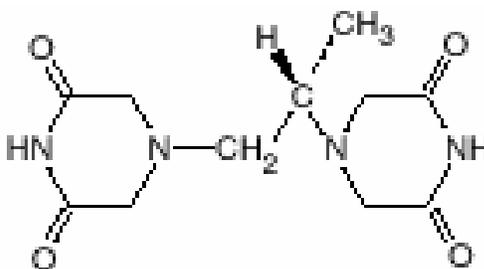
#### Drug Substance

Proper name: Dexrazoxane

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

Molecular formula and molecular mass: C<sub>11</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> and 268.28

Structural formula:



Physicochemical properties: ZINECARD (dexrazoxane) is a sterile, lyophilized, parenteral, cardioprotective agent for use in conjunction with anthracycline. It is a white to off-white crystalline powder.

It is sparingly soluble in water and 0.1 N HCl, slightly soluble in acetonitrile, ethanol, methanol and water/dimethylacetamide (1:1), and practically insoluble in non-polar organic solvents. Its melting range is 187-197°C. The acidic pK<sub>a</sub> value of dexrazoxane at 25°C is 2.1. The alkaline pK<sub>a</sub>'s are 10.1 and 11.1. The partition coefficient, expressed as the dexrazoxane concentration in 1-octanol divided by the aqueous phase concentration, is 0.025 at 25°C.

### CLINICAL TRIALS

The efficacy of ZINECARD 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 ZINECARD 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. Patients receiving ZINECARD 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<sup>2</sup> and reached statistical significance in patients

who received  $\geq 400$  mg/m<sup>2</sup> of doxorubicin. The studies also assessed the effect of the addition of ZINECARD 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 ZINECARD 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 ZINECARD with FAC was similar. More non-responders dropped out by course three in the ZINECARD arm. The non-responders correlated to dose delays due to additive myelotoxicity. It appears that ZINECARD may potentiate doxorubicin toxicity in some patients, thus causing increased early dropout rate or decreased dose-intensity.

Two of the randomized breast cancer studies evaluating the efficacy and safety of FAC with either ZINECARD or placebo were amended to allow patients on the placebo arm who had attained a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup> (six (6) courses of FAC) to receive FAC with open-label ZINECARD for each subsequent course. Most of these patients had already experienced a partial or complete response or had stable disease. Analyses of these amended studies indicate that significant though not complete cardioprotection can be obtained with the administration of ZINECARD only after the accumulated dose of 300 mg/m<sup>2</sup> 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 ZINECARD starting with the seventh course of FAC treatment.

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

Dexrazoxane has been shown to be effective in ameliorating the cardiotoxicity induced by anthracyclines, in mice, rats, hamsters, guinea pigs, rabbits, dogs and miniature swine. The Bertazzoli mouse model was utilized to induce cardiomyopathy over several weeks. The anthracycline was administered I.V. to ICRF Swiss mice twice weekly during weeks 1, 2, 5, 6 and 7. Dexrazoxane administered at dose ratios of 5, 10, 15 and 20 to 1, immediately prior to doxorubicin administration (4 mg/kg) significantly reduced the incidence of cardiomyopathy, scored from a scale of 1-4. There was a significant decrease in the incidence of moderate to severe lesions (scoring  $\geq 2$ ) at 5 to 1 dose ratio (64%) and a further response at 10 to 1 dose ratio (26%). The cardioprotective effect of doxorubicin at ratios of 15 and 20 to 1 were similar to that of 10 to 1.

Similar cardioprotective activity was seen with epirubicin- and idarubicin-treated mice. Cardiotoxicity at baseline was less severe with epirubicin (5 mg/kg) than with doxorubicin. Dexrazoxane was equally cardioprotective at dose ratios of 5, 10 and 20 to 1, which were more effective compared to the 1 to 1 ratio. Notably, at a ratio of 5 to 1, cardioprotection was equal to the other dose ratios. In mice treated with 1 mg/kg idarubicin, dexrazoxane was cardioprotective at dose ratios of 5, 10 and 20 to 1.

Dexrazoxane, although less than it is against the other anthracyclines, was also effective in ameliorating the cardiotoxicity caused by mitoxantrone in the mouse. A dose of 1.5 mg/kg

mitoxantrone administered I.V. per the Bertazzoli schedule, caused cardiomyopathy which was slightly less severe than that caused by doxorubicin at 4 mg/kg. At doses of 30 mg/kg and 15 mg/kg dexrazoxane, there were significant reductions in the mitoxantrone-induced cardiomyopathy.

In the foregoing mouse studies in which haematology, serum chemistry, and histopathology on major organs was performed, there were anthracycline-related non-cardiac toxicities including inhibition of weight gain and histomorphologic renal and liver changes. Dexrazoxane did not exert an appreciable effect on the other anthracycline toxicities.

Similarly, dexrazoxane exhibited a dose-dependent cardioprotective effect when administered to rats at a dose ratio of 5, 10 and 20 to 1, injected 30 minutes prior to I.V. administration of doxorubicin and epirubicin (1 mg/kg) once weekly for seven consecutive weeks.

The cardioprotective activity of dexrazoxane was convincingly demonstrated in the beagle dog. Every three weeks, beagle dogs were given dexrazoxane 25 mg/kg I.V. 15 minutes prior to a 1.75 mg/kg I.V. injection of doxorubicin. All of the dogs (n=8) given doxorubicin alone died after 7 or 8 courses.

Those given the combination of doxorubicin and dexrazoxane were still alive after 20 courses (67 weeks). Based on histological analysis, 100% of the dogs given doxorubicin alone, showed evidence of severe heart damage (score of 3+, severity scale (0-4). In dogs given the combination (n=8), no cardiac damage was observed in 50% of the animals, 25% had a score of 1 and the remainder had a score of 2.

Dogs pretreated with dexrazoxane received much higher cumulative doses of doxorubicin (35 - 43.75 mg/kg) than those receiving doxorubicin alone (12.25 - 14 mg/kg) and had significantly lower mean cardiomyopathy severity scores (0.75 versus 3.0).

Dexrazoxane appears to be highly schedule dependent, and the optimal cardioprotection is observed when dexrazoxane is given in a time span of 30 minutes prior to and 15 minutes after doxorubicin administration. However, studies in mice showed that dexrazoxane given I.V. as early as 2 hours prior to or as long as 1 hour after doxorubicin administration is cardioprotective. Simultaneous dosing of dexrazoxane also provided optimal protection in doxorubicin treated mice.

Dexrazoxane is intended for use with anthracycline chemotherapy or anthracycline containing combinations of cytotoxic drugs.

In several experimental tumour assays in the mouse, including leukemias and solid tumours, dexrazoxane was found to possess weak or no antitumour activity, in combination with such cytotoxic agents as doxorubicin, epirubicin, daunorubicin, mitoxantrone, 5-fluoruracil, cyclophosphamide, bleomycin, cisplatin, cytarabine, vincristine and methotrexate. In the P388 murine leukemia, L1210 leukemia models and Lewis lung carcinoma, dexrazoxane enhanced the antitumoural activity of doxorubicin as seen in the form of increased median survival time (MST) of mice. Dexrazoxane did not affect the antitumoural activity of optimal doxorubicin

dosages in the Gross leukemia, B16 melanoma, Madison 109 lung tumour in the mouse. At optimally efficacious doses of doxorubicin, dexrazoxane has no effect on the antitumoural activity of doxorubicin. At suboptimal doses, dexrazoxane may enhance the efficacy due to slight antitumoural activity it may possess.

The effect of dexrazoxane on the antitumoural efficacy of doxorubicin against human tumour xenografts was also investigated. At ratios of from 5:1 to 20:1 of dexrazoxane to doxorubicin, there was no interference with the efficacy of doxorubicin against fresh human tumour explants, the BL/LX5 human lung tumour cell line, or of the MX-1 breast cancer cell line implanted in the subrenal capsule of the mouse. However, at a ratio of 10:1, there was evidence of interference with the activity of doxorubicin against the BL/BX7 human mammary tumour (a subline of MX-1), implanted subcutaneously in the athymic mouse. Since this inhibitory effect was not seen at ratios of 5:1, 15:1 or 20:1, the significance of this observation is unclear.

In *in vitro* studies, there were additive or synergistic cytotoxic effects when combinations of dexrazoxane and doxorubicin were added to murine sarcoma 180 cells or HL-60 human leukemia cells.

Dexrazoxane was devoid of central nervous system activity (general behaviour, body and skin temperature) The acute hemodynamic effects of I.V. dexrazoxane were measured in anesthetized Beagle dogs. Dexrazoxane (80 and 200 mg/kg) had no consistent effects on mean arterial pressure, left ventricular pressure, contractility or heart rate.

*In vitro* studies in the rat, proved that dexrazoxane was devoid of effects on the autonomic nervous system. Intravenously in the rat, dexrazoxane reduce urinary  $K^+$  and  $Ca^{++}$  at doses of 100 mg/kg and above, and decreased urinary volume at 120 mg/kg.

With regard to immunological activity, dexrazoxane at doses of 100 mg/kg and above produced immunosuppression and can increase the immunosuppressive effects of doxorubicin in mice when given at 10 or 20 times the doxorubicin dose.

## 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 I.V. 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<sub>50</sub> 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<sub>50</sub> for doxorubicin alone was 16 and 23 mg/kg in males and females, respectively, whereas the LD<sub>50</sub> 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<sub>50</sub> of epirubicin alone in male and female mice, were 26 and 28 mg/kg, respectively, whereas in combination with dexrazoxane, the LD<sub>50</sub> 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<sub>50</sub> 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 I.V. 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 IV at doses of 10, 20 and 40 mg/kg approximately 25 minutes before an I.V. 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 at doses of 0.6, 1.2, and 2.4 mg/kg IV, 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 ZINECARD in animals.

**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.

**Teratology**

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.

## REFERENCES

1. Baldwin JR, Lewis RC, Narang PK. Plasma protein binding of ADR-529 in rat, rabbit, dog, and man. *Adria Labs Internal Report PK/DM-3154-91-11*; Study Director, Baldwin JR. 40p July 24, 1991.
2. Danesi R, Bernardini N, Macchiarini P, Del Tacca M. Doxorubicin cardio-toxicity is reduced by pretreatment with the iron chelator ADR-529. *Eur J Pharmacol* 1990; 182(5):1703.
3. Dardir M, Herman EH, Ferrans VJ. Effects of ICRF-187 on the cardiac and renal toxicity of epirubicin in spontaneously hypertensive rats. *Cancer Chemother Pharmacol* 1989; 23(5):269-275.
4. Earhart RH, Tutsch KD, Koeller JM, Rodriguez R, Robins HI, Vogel CL, Davis HL, Tormey DC. Pharmacokinetics of (+)-1,2-Di(3,5-dioxopiperazin-1-yl)propane intravenous infusions in adult cancer patients. *Cancer Res* 1982; 42(12):5255-5261.
5. Earhart RH, Tutsch K, Koeller JM, Robins HI, Davis HL, Tormey DC. Pharmacokinetics of ICRF-187 (NSC 169780) in man. *Proc Am Assoc Cancer Res* 1982; 23:128.
6. Hasinoff BB. The interaction of the cardioprotective agent ICRF-187 ((+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane); its hydrolysis product (ICRF-198); and other chelating agents with the Fe(III) and Cu(II) complexes of Adriamycin. *Agents Actions* 1989; 26(2/3):378-385.
7. Hasinoff BB. The iron(III) and copper(II) complexes of Adriamycin promote the hydrolysis of the cardioprotective agent ICRF-187 ((+)-1,2-Bis(3,5-dioxopiperazinyl-1-yl)propane). *Agents Actions* 1990;29(3/4):374-381.
8. Hasinoff BB, Reinders FX, Clark V. The enzymatic hydrolysis-activation of the adriamycin cardioprotective agent (+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane. *Drug Metab Dispos* 1991; 19(1):74-80.
9. Herman EH, Ferrans VJ. Amelioration of chronic anthracycline cardio-toxicity by ICRF-187 and other compounds. *Anticancer Drug Res* 1987; 2(1):92.
10. Hochster H, Liebes L, Sampathumaran R, Mendoza S, Wadler S, Speyer J, Blum R, Reynolds R, Narang PK, Lewis R. Pharmacokinetics (PK) of adriamycin (DOX) and escalating ADR 529 in combination. *Proc Am Soc Clin Oncol* 1991; 10:100.
11. Hochster H, Speyer J, Liebes L, Oratz R, Meyers M, Alba S, Wadler S, Reynolds R, Narang PK, Blum R. Phase I & pharmacokinetic study of escalating ADR-529 (ICRF-187) with doxorubicin (adriamycin). *Proc Am Soc Clin Oncol* 1990; 9:82.

12. Holcenberg JS, Tutsch KD, Earhart RH, Ungerleider RS, Kamen BA, Pratt CB, Gribble TJ, Glaubiger DL. Phase I study of ICRF-187 in paediatric cancer patients and comparison of its pharmacokinetics in children and adults. *Cancer Treat Rep* 1986; 70(6):703-709.
13. Kaiser J-D, Vigneron J, Zenier H, et al. Chemical and physical stability of Dexrazoxane, dilute with Ringer's Lactate solution, in polyvinyl and polyethylene containers. *EJHP Science* 2007; 13(3):55-9.
14. Marty M, Espie M, Llombart A, et al. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane®) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Annals of Oncology* 2006;17(4):614-22.
15. Ryan TP, Samokyszyn VM, Dellis S, Aust SD. Effects of (+)-1,2-bis(3,5-dioxopiperazin-1-yl)propane (ADR-529) on iron-catalyzed lipid per-oxidation. *Chem Res Toxicol* 1990; 3(4):384-390.
16. Verhoef V, Colborn D, Bell V, Filppi J. Cardioprotective activity of ADR-529 for daunorubicin and idarubicin. *Proc Am Assoc Cancer Res* 1990; 31:404.
17. Verhoef V, Bell V, Filppi J. Effect of the cardioprotective agent ADR-529 (ICRF-187) on the antitumour activity of doxorubicin. *Proc Am Assoc Cancer Res* 1988; 29:A1083.
18. Vile GF, Winterbourn CC. dl-N-N'-Dicarboxamidomethyl-N,N'-dicarboxymethyl-1,2-diaminopropane (ICRF-198) and d-1,2-Bis(3,5-dioxopiperazine-1-yl)propane (ICRF-187) inhibition of Fe<sup>3+</sup> reduction, lipid peroxidation, and CaATPase inactivation in heart microsomes exposed to Adriamycin. *Cancer Res* 1990; 50(8):2307-2310.
19. Vogel CL, Gorowski E, Davila E, Eisenberger M, Kosinski J, Agarwal RP, Savaraj N. Phase I clinical trial and pharmacokinetics of weekly ICRF-187 (NSC 169780) infusion in patients with solid tumours. *Invest New Drugs* 1987; 5(2): 187-198.
20. Vogel C, Davila E, Agarwal R, Gorowski E, Savaraj N. Phase I trial and pharmacokinetics of weekly ICRF-187: a Southeastern cancer study group pilot. *Proc Am Soc Clin Oncol* 1986; 5:35.

**PART III: CONSUMER INFORMATION**

**ZINECARD  
Dexrazoxane for Injection**

This leaflet is part III of a three-part "Product Monograph" published when ZINECARD was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZINECARD. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

ZINECARD is used to reduce or prevent the incidence and severity of the heart damage (cardiotoxicity) caused by doxorubicin in women with metastatic breast cancer.

**What it does:**

ZINECARD penetrates cell membranes to protect the heart muscle from anthracycline-induced cardiotoxicity by interfering with iron-mediated free radical generation.

**When it should not be used:**

ZINECARD should not be used in patients who are allergic to dexrazoxane or components of the container of ZINECARD.

ZINECARD is not indicated for use in patients under 18 years of age.

You should not receive ZINECARD if your cancer treatment does not include doxorubicin.

ZINECARD is not an anticancer drug.

**What the medicinal ingredient is:**

Dexrazoxane.

**What the important nonmedicinal ingredients are:**

There are no other ingredients.

**What dosage forms it comes in:**

ZINECARD is a lyophilized powder for injection. It is available in vials of 250 mg or 500 mg.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

- **If you are prescribed ZINECARD, it will only be given to you by doctors or nurses experienced in giving chemotherapy.**
- **ZINECARD can add to the bone marrow lowering effects of chemotherapy. This can weaken your immune system, making it easier for you to get sick from being around others who are ill.**
- **Using ZINECARD while you are pregnant can harm your unborn baby, so you should avoid becoming pregnant and use effective birth control. If you think you have become pregnant while using this medicine, tell your doctor right away.**
- **To be sure this medication is not causing harmful effects, your blood cells and liver and kidney function will need to be tested often. Do not miss any follow up visits to your doctor for blood or urine tests.**

ZINECARD may increase the risk of having:

- An infection (due to low white blood cell count)
- Leukaemia (cancer of the blood)
- Blood clots
- An allergic reaction (hives; difficulty breathing; swelling of your face, lips, tongue, or throat)

**BEFORE you use ZINECARD talk to your doctor or pharmacist if you:**

- Have liver problems
- Have kidney problems
- Have heart problems
- Are pregnant or plan to become pregnant
- Are breastfeeding

**INTERACTIONS WITH THIS MEDICATION**

Some cancer medications may be less effective if they are used with ZINECARD. Tell your doctor if your chemotherapy medications include:

- fluorouracil
- cyclophosphamide

This list is not complete and other drugs may interact with dexrazoxane. Tell your doctor about all medications you use. This includes prescription, over-the-counter, vitamin, and herbal products. Do not start a new medication without telling your doctor.

**PROPER USE OF THIS MEDICATION**

ZINECARD is injected in to a vein through an IV. You will receive this injection in a clinic or hospital setting.

ZINECARD is to be given to you as a rapid intravenous infusion, between 15 to 30 minutes before the treatment with doxorubicin.

**Usual dose:** the recommended dosage ratio for ZINECARD and doxorubicin is 10:1 or 500 mg/m<sup>2</sup> ZINECARD given before the 50 mg/m<sup>2</sup> doxorubicin.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The most common side effects (affecting more than 10 out of every 100 people) include:

- low blood cell count
- hair loss
- nausea, vomiting, diarrhea
- tiredness
- anorexia
- mouth sores
- fever, infection
- damage to nerve tissue
- pain at the injection site

Common side effects (affecting between 1 and 10 of every 100 people) include:

- redness of the blood vessels
- difficulty swallowing
- swelling of a vein
- itching
- burning sensation of the esophagus
- bleeding
- tissue swelling, redness and pain at the injection site
- skin reaction in the areas previously exposed to other agents
- heart failure

If any of the side effects get serious or if you notice any side effect not listed in this leaflet, please tell your doctor.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Low concentration of granulocytes in the blood - a type of white blood cells		√	

*This is not a complete list of side effects. For any unexpected effects while taking ZINECARD, contact your doctor or pharmacist.*

**HOW TO STORE IT**

ZINECARD lyophilized powder for injection should be stored at controlled room temperature, 15-30°C. 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. 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.Pfizer.ca> or by contacting Pfizer Canada Inc. Medical Information at 1-800-463-6001.

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