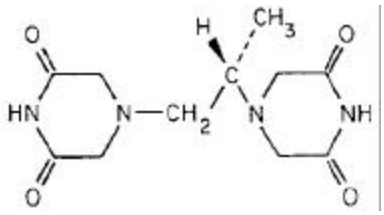
Zinecard®
dexrazoxane for injection

DESCRIPTION

ZINECARD® (dexrazoxane for injection) is a sterile, pyrogen-free lyophilizate intended for intravenous administration. It is a cardioprotective agent for use in conjunction with doxorubicin.

Chemically, dexrazoxane is (S)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione. The structural formula is as follows:



$C_{11}H_{16}N_4O_4$ M.W. 268.28

Dexrazoxane, a potent intracellular chelating agent is a derivative of EDTA. Dexrazoxane is a whitish crystalline powder which melts at 191° to 197°C. It is sparingly soluble in water and 0.1 N HCl, slightly soluble in ethanol and methanol and practically insoluble in nonpolar organic solvents. The pK_a is 2.1. Dexrazoxane has an octanol/water partition coefficient of 0.025 and degrades rapidly above a pH of 7.0.

ZINECARD is available in 250 mg and 500 mg single use only vials.
Each **250 mg vial** contains dexrazoxane hydrochloride equivalent to 250 mg dexrazoxane. Hydrochloric Acid, NF is added for pH adjustment. When reconstituted as directed with the 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP diluent provided, each mL contains: 10 mg dexrazoxane. The pH of the resultant solution is 3.5 to 5.5.
Each **500 mg vial** contains dexrazoxane hydrochloride equivalent to 500 mg dexrazoxane. Hydrochloric Acid, NF is added for pH adjustment. When reconstituted as directed with the 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP diluent provided, each mL contains: 10 mg dexrazoxane. The pH of the resultant solution is 3.5 to 5.5.

CLINICAL PHARMACOLOGY

Mechanism of Action: The mechanism by which ZINECARD exerts its cardioprotective activity is not fully understood. Dexrazoxane is a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring-opened chelating agent that interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy.

Pharmacokinetics: The pharmacokinetics of dexrazoxane have been studied in advanced cancer patients with normal renal and hepatic function. Generally, the pharmacokinetics of dexrazoxane can be adequately described by a two-compartment open model with first-order elimination. Dexrazoxane has been administered as a 15 minute infusion over a dose-range of 60 to 900 mg/m^2 with 60 mg/m^2 of doxorubicin, and at a fixed dose of 500 mg/m^2 with 50 mg/m^2 doxorubicin. The disposition kinetics of dexrazoxane are dose-independent, as shown by linear relationship between the area under

plasma concentration-time curves and administered doses ranging from 60 to 900 mg/m^2. The mean peak plasma concentration of dexrazoxane was 36.5 µg/mL at the end of the 15 minute infusion of a 500 mg/m^2 dose of ZINECARD administered 15 to 30 minutes prior to the 50 mg/m^2 doxorubicin dose. The important pharmacokinetic parameters of dexrazoxane are summarized in the following table.

SUMMARY OF MEAN (%CV[a]) DEXRAZOXANE PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF 10:1 OF ZINECARD: DOXORUBICIN

Dose Doxorubicin (mg/m^2)	Dose Zinecard (mg/m^2)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance (L/h/m^2)	Renal Clearance (L/h/m^2)	[b]Volume of Distribution (L/m^2)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

[a] Coefficient of variation

[b] Steady-state volume of distribution

Following a rapid distributive phase (~0.2 to 0.3 hours), dexrazoxane reaches postdistributive equilibrium within two to four hours. The estimated steady-state volume of distribution of dexrazoxane suggests its distribution primarily in the total body water (25 L/m^2). The mean systemic clearance and steady-state volume of distribution of dexrazoxane in two Asian female patients at 500 mg/m^2 dexrazoxane along with 50mg/m^2 doxorubicin were 15.15 L/h/m^2 and 36.27 L/m^2, respectively, but their elimination half-life and renal clearance of dexrazoxane were similar to those of the ten Caucasian patients from the same study. 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. The metabolite levels were not measured in the pharmacokinetic studies.

Urinary excretion plays an important role in the elimination of dexrazoxane. Forty-two percent of the 500 mg/m^2 dose of ZINECARD was excreted in the urine.

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

Special Populations:

Pediatric: The pharmacokinetics of ZINECARD have not been evaluated in pediatric patients.

Gender: Analysis of pooled data from two pharmacokinetic studies indicate that male patients have a lower mean clearance value than female patients (110 ml/min/m^2 versus 133 ml/min/m^2). This gender effect is not clinically relevant.

Renal insufficiency: The pharmacokinetics of ZINECARD have not been evaluated in patients with renal impairment.

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 (see Dosage and Administration). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage is proportionately reduced in patients with hepatic impairment.

Drug Interactions: There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m^2) and its predominant metabolite, doxorubicinol, in the presence of dexrazoxane (500 mg/m^2) in a crossover study in cancer patients.

CLINICAL STUDIES

The ability of ZINECARD to prevent/reduce the incidence and severity of doxorubicin-induced cardiomyopathy was demonstrated in three prospectively randomized placebo-controlled studies. In these studies, patients were treated with a doxorubicin-containing regimen and either ZINECARD or placebo starting with the first course of chemotherapy. There was no restriction on the cumulative dose of doxorubicin. 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^2 and reached statistical significance in patients who received ≥400 mg/m^2 of doxorubicin. In addition to evaluating the effect of ZINECARD on cardiac function, the studies also assessed the effect of the addition of ZINECARD on the anti-tumor efficacy of the chemotherapy regimens. In one study (the largest of three breast cancer studies) patients with advanced breast cancer receiving fluorouracil, doxorubicin and cyclophosphamide (FAC) with ZINECARD had a lower response rate (48% vs 63%; p=0.007) and a shorter time to progression than patients who received FAC + placebo, although the survival of patients who did or did not receive ZINECARD with FAC was similar.

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^2 (six courses of FAC) to receive FAC with open-label ZINECARD for each subsequent course. This change in design allowed examination of whether there was a cardioprotective effect of ZINECARD even when it was started after substantial exposure to doxorubicin.

Retrospective historical analyses were then performed to compare the likelihood of heart failure in patients to whom ZINECARD was added to the FAC regimen after they had received six (6) courses of FAC (and who then continued treatment with FAC therapy) with the heart failure rate in patients who had received six (6) courses of FAC and continued to receive this regimen without added ZINECARD. These analyses showed that the risk of experiencing a cardiac event (see Table 1 for definition) at a given cumulative dose of doxorubicin above 300 mg/m^2 was substantially greater in the 99 patients who did not receive ZINECARD beginning with their seventh course of FAC than in the 102 patients who did receive ZINECARD (See Figure 1).

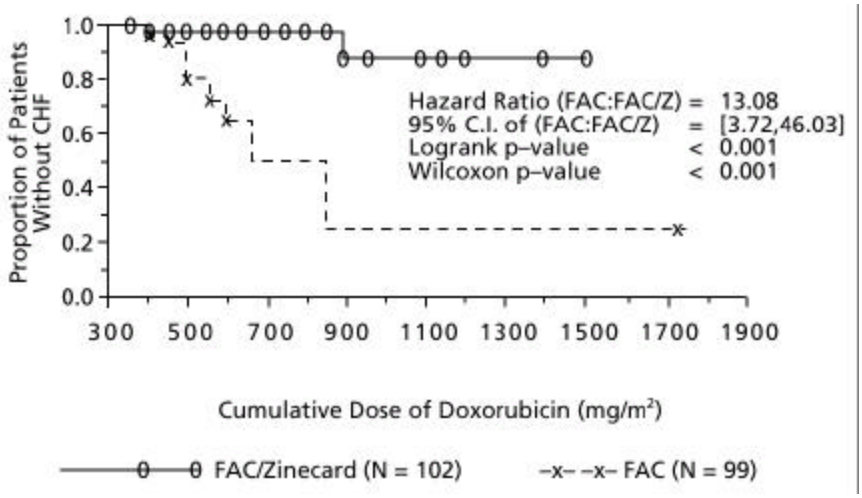
Table 1
The development of cardiac events is shown by:

1. Development of congestive heart failure, defined as having two or more of the following:
   a. Cardiomegaly by X-ray
   b. Basilar Rales
   c. S_3 Gallop
   d. Paroxysmal nocturnal dyspnea and/or orthopnea and/or significant dyspnea on exertion.
2. Decline from baseline in LVEF by ≥10% and to below the lower limit of normal for the institution.
3. Decline in LVEF by ≥20% from baseline value.
4. Decline in LVEF to ≥5% below lower limit of normal for the institution.

Figure 1 displays the risk of developing congestive heart failure by cumulative dose of doxorubicin in patients who received ZINECARD starting with their seventh course of FAC compared to patients who did not. Patients unprotected by ZINECARD had a 13 times greater risk of developing

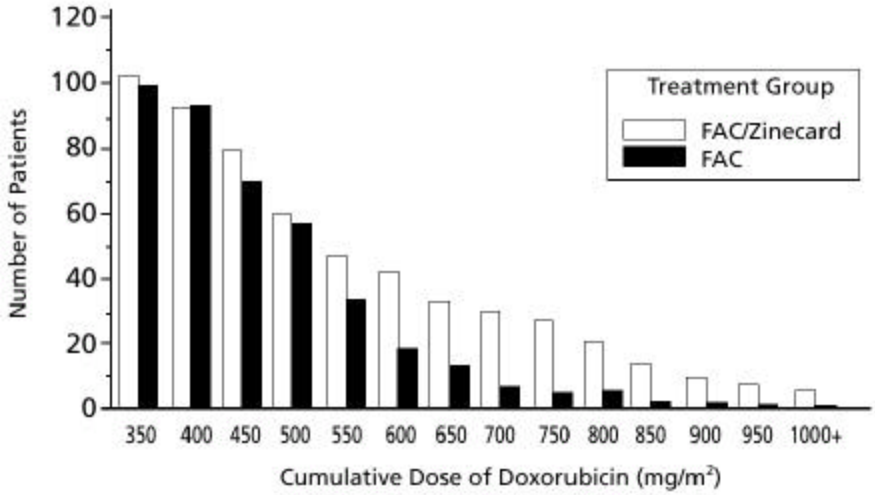
congestive heart failure. Overall, 3% of patients treated with ZINECARD developed CHF compared with 22% of patients not receiving ZINECARD.

Figure 1
Doxorubicin Dose at Congestive Heart Failure (CHF)
FAC vs. FAC/ZINECARD Patients
Patients Receiving At Least Seven Courses of Treatment



Because of its cardioprotective effect, ZINECARD permitted a greater percentage of patients to be treated with extended doxorubicin therapy. Figure 2 shows the number of patients still on treatment at increasing cumulative doses.

Figure 2
Cumulative Number of Patients On Treatment
FAC vs. FAC/ZINECARD Patients
Patients Receiving at Least Seven Courses of Treatment



In addition to evaluating the cardioprotective efficacy of ZINECARD in this setting, the time to tumor progression and survival of these two groups of patients were also compared. There was a similar time to progression in the two groups and survival was at least as long for the group of patients that received ZINECARD starting with their seventh course, i.e., starting after a cumulative

dose of doxorubicin of 300 mg/m^2. These time to progression and survival data should be interpreted with caution, however, because they are based on comparisons of groups entered sequentially in the studies and are not comparisons of prospectively randomized patients.

INDICATIONS AND USAGE

ZINECARD is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy (see WARNINGS).

CONTRAINDICATIONS

ZINECARD should not be used with chemotherapy regimens that do not contain an anthracycline.

WARNINGS

ZINECARD may add to the myelosuppression caused by chemotherapeutic agents.

There is some evidence that the use of dexrazoxane concurrently with the initiation of fluorouracil, doxorubicin and cyclophosphamide (FAC) therapy interferes with the antitumor efficacy of the regimen, and this use is not recommended. In the largest of three breast cancer trials, patients who received dexrazoxane starting with their first cycle of FAC therapy had a lower response rate (48% vs 63%; p=0.007) and shorter time to progression than patients who did not receive dexrazoxane (see **Clinical Studies** section of **CLINICAL PHARMACOLOGY**). Therefore, ZINECARD should only be used in those patients who have received a cumulative doxorubicin dose of 300 mg/m^2 and are continuing with doxorubicin therapy.

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^2 without ZINECARD, does not eliminate the potential for anthracycline induced cardiac toxicity. Therefore, cardiac function should be carefully monitored.

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.

PRECAUTIONS

General

Doxorubicin should not be given prior to the intravenous injection of ZINECARD. ZINECARD should be given by slow I.V. push or rapid drip intravenous infusion from a bag. Doxorubicin should

be given within 30 minutes after beginning the infusion with ZINECARD. (See **DOSAGE AND ADMINISTRATION**).

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 mild, additive effects upon the myelosuppressive activity of chemotherapeutic agents may occur.

Laboratory tests

As ZINECARD may add to the myelosuppressive effects of cytotoxic drugs, frequent complete blood counts are recommended. (See **ADVERSE REACTIONS**).

Drug Interactions

ZINECARD does not influence the pharmacokinetics of doxorubicin.

Carcinogenesis, Mutagenesis, Impairment of Fertility (see **WARNINGS** section for information on human carcinogenicity)

No long-term carcinogenicity studies have been carried out with dexrazoxane in animals. Dexrazoxane was not mutagenic in the Ames test but was found to be clastogenic to human lymphocytes in vitro and to mouse bone marrow erythrocytes in vivo(micronucleus test).

The possible adverse effects of ZINECARD on the fertility of humans and experimental animals, male or female, have not been adequately studied. Testicular atrophy was seen with dexrazoxane administration at doses as low as 30 mg/kg weekly for 6 weeks in rats (1/3 the human dose on a mg/m^2 basis) and as low as 20 mg/kg weekly for 13 weeks in dogs (approximately equal to the human dose on a mg/m^2 basis).

Pregnancy - *Pregnancy Category C*

Dexrazoxane was maternotoxic at doses of 2 mg/kg (1/40 the human dose on a mg/m^2 basis) and embryotoxic and teratogenic at 8 mg/kg (approximately 1/10 the human dose on a mg/m^2 basis) when given daily to pregnant rats during the period of organogenesis. Teratogenic effects in the rat included imperforate anus, microphthalmia, and anophthalmia. In offspring allowed to develop to maturity, fertility was impaired in the male and female rats treated in utero during organogenesis at 8 mg/kg. In rabbits, doses of 5 mg/kg (approximately 1/10 the human dose on a mg/m^2 basis) daily during the period of organogenesis were maternotoxic and dosages of 20 mg/kg (1/2 the human dose on a mg/m^2 basis) were embryotoxic and teratogenic. Teratogenic effects in the rabbit included several skeletal malformations such as short tail, rib and thoracic malformations, and soft tissue variations including subcutaneous, eye and cardiac hemorrhagic areas, as well as agenesis of the gallbladder and of the intermediate lobe of the lung. There are no adequate and well-controlled studies in pregnant women. ZINECARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dexrazoxane 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 exposed to dexrazoxane, mothers should be advised to discontinue nursing during dexrazoxane therapy.

Pediatric Use

Safety and effectiveness of dexrazoxane in pediatric patients have not been established.

Geriatric Use

Clinical studies of ZINECARD did not include sufficient numbers of subjects aged 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.

ADVERSE REACTIONS

ZINECARD at a dose of 500 mg/m^2 has been administered in combination with FAC in randomized, placebo-controlled, double-blind studies to patients with metastatic breast cancer. The dose of doxorubicin was 50 mg/m^2 in each of the trials. Courses were repeated every three weeks, provided recovery from toxicity had occurred. Table 2 below lists the incidence of adverse experiences for patients receiving FAC with either ZINECARD or placebo in the breast cancer studies. Adverse experiences occurring during courses 1 through 6 are displayed for patients receiving ZINECARD or placebo with FAC beginning with their first course of therapy (column 1 & 3, respectively). Adverse experiences occurring at course 7 and beyond for patients who received placebo with FAC during the first six courses and who then received either ZINECARD or placebo with FAC are also displayed (column 2 & 4, respectively).

Table 2

ADVERSE EXPERIENCE	PERCENTAGE (%) OF BREAST CANCER PATIENTS WITH ADVERSE EXPERIENCE			
	FAC + ZINECARD		FAC + PLACEBO	
	Courses 1-6 N = 413	Courses ≥ 7 N = 102	Courses 1-6 N = 458	Course ≥ 7 N = 99
Alopecia	94	100	97	98
Nausea	77	51	84	60
Vomiting	59	42	72	49
Fatigue/Malaise	61	48	58	55
Anorexia	42	27	47	38
Stomatitis	34	26	41	28
Fever	34	22	29	18
Infection	23	19	18	21
Diarrhea	21	14	24	7
Pain on Injection	12	13	3	0
Sepsis	17	12	14	9
Neurotoxicity	17	10	13	5
Streaking/Erythema	5	4	4	2
Phlebitis	6	3	3	5
Esophagitis	6	3	7	4
Dysphagia	8	0	10	5
Hemorrhage	2	3	2	1
Extravasation	1	3	1	2
Urticaria	2	2	2	0
Recall Skin Reaction	1	1	2	0

The adverse experiences listed above are likely attributable to the FAC regimen with the exception of pain on injection that was observed mainly on the ZINECARD arm.

Myelosuppression

Patients receiving FAC with ZINECARD experienced more severe leucopenia, granulocytopenia and thrombocytopenia at nadir than patients receiving FAC without ZINECARD, but recovery counts were similar for the two groups of patients.

Hepatic and Renal

Some patients receiving FAC + ZINECARD or FAC + placebo experienced marked abnormalities in hepatic or renal function tests, but the frequency and severity of abnormalities in bilirubin, alkaline phosphatase, BUN, and creatinine were similar for patients receiving FAC with or without ZINECARD.

OVERDOSAGE

There have been no instances of drug overdose in the clinical studies sponsored by either Pharmacia & Upjohn Company or the National Cancer Institute. The maximum dose administered during the cardioprotective trials was 1000 mg/m^2 every three weeks.

Disposition studies with ZINECARD have not been conducted in cancer patients undergoing dialysis, but 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 it could be removed using conventional peritoneal or hemodialysis.

There is no known antidote for dexrazoxane. 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.

DOSAGE AND ADMINISTRATION

The recommended dosage ratio of ZINECARD:doxorubicin is 10:1 (eg, 500 mg/m^2 ZINECARD:50 mg/m^2 doxorubicin). Since a doxorubicin dose reduction is recommended in the presence of hyperbilirubinemia, the ZINECARD dosage should be proportionately reduced (maintaining the 10:1 ratio) in patients with hepatic impairment. ZINECARD must be reconstituted with 0.167 Molar (M/6) Sodium Lactate Injection, USP, to give a concentration of 10 mg ZINECARD for each mL of sodium lactate. The reconstituted solution should be given by slow I.V. push or rapid drip intravenous infusion from a bag. After completing the infusion of ZINECARD, and prior to a total elapsed time of 30 minutes (from the beginning of the ZINECARD infusion), the intravenous injection of doxorubicin should be given.

Reconstituted ZINECARD, when transferred to an empty infusion bag, is stable for 6 hours from the time of reconstitution when stored at controlled room temperature, 15° to 30°C (59° to 86°F) or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

The reconstituted ZINECARD solution may be diluted with either 0.9% Sodium Chloride Injection, USP or 5.0% Dextrose Injection, USP to a concentration range of 1.3 to 5.0 mg/mL in intravenous

infusion bags. The resultant solutions are stable for 6 hours when stored at controlled room temperature, 15° to 30°C (59° to 86°F) or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

Incompatibility

ZINECARD should not be mixed with other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Handling and Disposal: Caution in the handling and preparation of the reconstituted solution must be exercised and the use of gloves is recommended. If ZINECARD powder or solutions contact the skin or mucosae, immediately wash thoroughly with soap and water.

Procedures normally used for proper handling and disposal of anti-cancer drugs should be considered for use with ZINECARD. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

ZINECARD® (dexrazoxane for injection) is available in the following strengths as sterile, pyrogen-free lyophilizates.

NDC 0013-8715-62 — 250 mg single dose vial with a red flip-top seal, packaged in single vial packs.
(This package also contains a 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP.)

NDC 0013-8725-89 — 500 mg single dose vial with a blue flip-top seal, packaged in single vial packs.
(This package also contains a 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, USP.)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Reconstituted solutions of ZINECARD are stable for 6 hours at controlled room temperature or under refrigeration, 2° to 8°C (36° to 46°F). DISCARD UNUSED SOLUTIONS.

Rx only

REFERENCES:

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2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC: Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institutes of Health; 1992. US Dept of Health and Human Services, Public Health Service Publication NIH 92-2621.

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4. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

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7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.

8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). *Am J Health-Syst Pharm.* 1996;53-1669-1685.

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