Physician's Prescribing Information

CARDIOXANE

Composition : CARDIOXANE contains 500 mg lyophilized dexrazoxane, as its hydrochloride salt. The chemical name of dexrazoxane is (S)-(+)-1,2 bis(3,5-dioxopiperazinyl)propane, its commonly called code name ICRF-187. Dexrazoxane, a potent intracellular chelating agent is a derivative of EDTA. Dexrazoxane is a whitish crystalline powder which melts at 191ºC to 197ºC, it is sparingly soluble in nonpolar organic solvents. The pK_a is 2.1. Dexrazoxane has an octanol/water partition coefficient of 0.025 and degrades rapidly above pH of 7.0.

CLINICAL PHARMACOLOGY

Mechanism of Action: the mechanism by which CARDIOXANE 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 60-900 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 60-900 mg/m^2. The mean peak plasma concentration of Dexrazoxane was 36.5µg/mL at the end of the 15 minute infusion of a 500 mg/m^2 dose of CARDIOXANE administered 15 to 30 minutes prior to the 50 mg/m^2 doxorubicin dose. Following a rapid distributive phase (~0.2-0.3 hours), Dexrazoxane reaches post-distributive equilibrium within two to four hours. The estimated steady state volume of distribution of Dexrazoxane suggests its distribution primarily in the total body water (5L/m^2). The mean systemic clearance and a steady state volume of distribution of Dexrazoxane in two Asian female patients of 500 mg/m^2 Dexrazoxane along with 50 mg/m^2 doxorubicin were 15.15L/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 ten Caucasian patients from the same study. Qualitative metabolism studies with CARDIOXANE 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 phamacokinetic studies. Urinary excretion plays an important role in the elimination of Dexrazoxane. Forty two percent of the 500 mg/m^2 dose of CARDIOXANE was excreted in the urine.

Protein binding: *in vitro* studies have shown CARDIOXANE is not bound to plasma proteins.

Special populations: the pharmacokinetics of CARDIOXANE have not been evaluated in pediatric populations nor in hepatic or renal insufficiency patients.

Clinical studies : the ability of CARDIOXANE to prevent / reduce the incidence and severity of doxorubicin- induced cardiomyopathy was demonstrated in three prospectively randomized placebo-controlled studies. In theses studies, patients were treated with a doxorubicin – containing regimen and either CARDIOXANE 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 (LVEF), utilizing resting multigated function nuclear medicine (MUGA) scans, and by clinical evaluations. Patients receiving CARDIOXANE had significantly smaller mean decreases from baseline in LVEF and lower incidence of congestive heart failure that 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 CARDIOXANE on cardiac function, the studies also assessed the effect of the addition of CARDIOXANE on the antitumor 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 CARDIOXANE 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 no receive CARDIOXANE with FAC was similar.

Two of the randomized breast cancer studies evaluating the efficacy and safety of FAC with either CARDIOXANE 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 CARDIOXANE for each subsequent course. This change in design allowed examination of whether there was a cardioprotective effect of CARDIOXANE 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 CARDIOXANE was added to the FAC regiment after they had received six (6) courses of FAC (and who then continued treatment with FAC therapy) with the heart failure in patients who had received 6 (six) courses of FAC and continued to receive this regimen without added CARDIOXANE. 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 CARDIOXANE beginning with their seventh course of FAC than in the 102 patients who did receive CARDIOXANE.

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 from baseline in LVEF by ≥ 20% from baseline value
4. Decline in LVEF to ≥ 5% below lower limit of normal for the institution

Because of its cardioprotective effect, CARDIOXANE permitted a greater percentage of patients to be treated with extended doxorubicin therapy.

In addition to evaluating the cardioprotective efficacy of CARDIOXANE 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 CARDIOXANE starting with the 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

CARDIOXANE is indicated for the prevention of cardiotoxicity in women with breast cancer at high risk of heart failure receiving doxorubicin-containing therapy.

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

WARNINGS

CARDIOXANE may add to the myelosupresion caused by chemotherapeutic agents. Although clinical studies have shown that patients receiving FAC with CARDIOXANE May receive a higher cumulative dose of doxorubicin before experiencing cardiac toxicity than patients receiving FAC without CARDIOXANE, the use of CARDIOXANE in patients who have already received a cumulative dose of doxorubicin of 300 mg/m^2 without CARDIOXANE,

DOES NOT ELIMINATE THE POTENTIAL OF 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- 480 GRAMS AND THE DURATION OF TREATMENT WAS FROM 42 TO 319 WEEKS. ONCE CSE OF T-CELL LYMPHOMA, A CSE 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 CARDIOXANE. CARDIOXANE 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 CARDIOXANE (see **dosage and administration**).
As CARDIOXANE will always be used with cytotoxic drugs, patients should be monitored closely. While the myelosupressive effects of CARDIOXANE at the recommended dose are mild, additive effects upon the myelosupressive activity of chemotherapeutic agents may occur.

Laboratory tests
As CARDIOXANE may add to the myelosupressive effects of cytotoxic drugs, frequent complete blood counts are recommended. (see **Adverse reactions)**

Drug interactions

There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m^2 and its predominant metabolite, doxorubinicinol, in the presence of Dexrazoxane (500 mg/m^2) in a crossover study in cancer patients. (See also **Actions/clinical pharmacology)**
CARDIOXANE does not influence the pharmacokinetics of doxorubicin.

Carcinogenesis, Mutagenesis, Impairment to 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 CARDIOXANE on the fertility of humans and experimental animals, male or female, have not been adequately studied. Testicular atrophy was seen with Dexrazoxane administration at dose 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 2mg/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, microphtalmia , and anophtalmia. 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 5mg/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 tall, rib and thoracic malformations,and soft tissue variation 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. CARDIOXANE should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

Nursing mothers- it is not known whether Dexrazoxane is 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 children has not been established.

ADVERSE REACTIONS

CARDIOXANE 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 CARDIOXANE or placebo in the breast cancer studies. Adverse experiences occurring during courses 1 to 6 displayed for patients receiving CARDIOXANE or placebo with FAC beginning with their first course if 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 CARDIOXANE or placebo with FAC are also displayed (columns 2& 4 respectively).

TABLE 2
PERCENTAGE (%) OF BREAST CANCER PATIENTS WITH ADVERSE EXPERIENCES

ADVERSE EXPERIENCE	FAC +CARDIOXANE		FAC + PLACEBO	
	COURSES 1-6 N= 413	COURSES≥7 N = 102	COURSES 1-6 N= 458	COURSES≥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/ERYHTEMA	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 manly on the CARDIOXANE arm.

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

Hepatic and renal- some patients receiving FAC+CARDIOXANE or FAC +placebo experienced marked abnormalities in hepatic or renal function tests, but the frequency and severity of abnormalities in billirubin, alkaline phosphatase , BUN , and creatinine were similar for patients receiving FAC with or without CARDIOXANE.

POSOLOGY AND METHOD OF ADMINISTRATION

CARDIOXANE is administered by short intravenous infusion over 15 minutes, approximately 30 minutes prior to doxorubicin administration at a dose level 20 times the doxorubicin dose level. It is recommended that CARDIOXANE is given at a dose of 100 mg/m^2 when the commonly used dosage schedule for doxorubicin of 50 mg/m^2 every 21 days is employed, however the total dose of CARDIOXANE should never exceed the 1000 mg/m^2/d.
CARDIOXANE treatment should be initiated simultaneously with the first dose of doxorubicin and should be repeated each time doxorubicin is administered.
There are no special dosage recommendations for the elderly.
Safety and efficacy of CARDIOXANE in children have not been established.
For reconstitution the contents of each vial should be dissolved in 25 ml Sterile Water for Injections. The vial contents will dissolve within a few minutes with gentle shaking. The resultant solution has a pH of approximately 1.6 . To avoid the risk of thrombophlebitis at the injection site CARDIOXANE should not be infused without further dilution.
The contents of the appropriate number of vials should be mixed aseptically and diluted to a volume of 200-250 ml. with ringer Lactate Solution , 0.16 M Sodium lactate USP or phosphate buffer.
Note: parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

OVERDOSAGE
Signs and symptoms of overdosage are likely to consist of leukopenia, throbocytopenia, nausea, vomiting, diarrhea, skin reactions and alopecia. There is no specific antidote and treatment should be symptomatic.

Special warnings

CARDIOXANE should only be administered to patients undergoing therapy with doxorubicin-containing chemotherapy regimens.
Hematological monitoring should be undertaken regularly, particularly during the first two cycles of therapy.
Leukopenia and thrombocytopenia reverse quickly on cessation of therapy. To ensure that the full cardioprotective potential of CARDIOXANE is realized , it is essential that CARDIOXANE treatment is started at the time of the first dose of doxorubicin.

Effects on the ability to drive and use machines

It is unlikely that CARDIOXANE will affect the ability to drive or use machines, as it has not been found to have any effects on the central nervous system.

PHARMACEUTICAL PARTICULARS
Incompatibilities –incompatibilities with other drugs or materials are not known.
CARDIOXANE should however not be mixed with other drugs during infusion.

Shelf life –CARDIOXANE should not be stored beyond the expiration date amrked in the vials and the carton. Since CARDIOXANE contains no antimicrobial preservatives it is recommended to start the administration of the solution promptly after reconstitution/dilution.

Special precautions for storage- store the lyophilized product below 25ºC. protect from light and moisture. The diluted product should be stored protected from light at 2-8ºC and used within 4 hours. Any unused solution should be discarded.

Nature and content of the container – CARDIOXANE is packed in single use 36 ml vials of brown light- resistant type I glass , closed with a chlorobutyl rubber stopper and an aluminium flip-off cap. Each vial contains 500 mg of the active ingredient in its hydrochloride form.
Manufacturer : Chiron BV Paasheuvelweg 30, 1105 BJ Amsterdam, The Netherlands
Agent: Megapharm Ltd. PO Box 519 Hod Hasharon 45105 Israel

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