

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CARDIOXANE[®] 500mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 500 mg of dexrazoxane as its hydrochloride salt.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Sterile, pyrogen free, white to off-white, lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardioxane is indicated in adults for the prevention of chronic cumulative cardiotoxicity caused by anthracycline use in advanced and/or metastatic breast cancer patients who have received a prior cumulative dose of 300 mg/m² of doxorubicin or a prior cumulative dose of 540 mg/m² of epirubicin when further anthracycline treatment is required.

4.2 Posology and method of administration

Posology

Cardioxane is administered by a short intravenous infusion (15 minutes), approximately 30 minutes prior to anthracycline administration at a dose equal to

10 times the doxorubicin-equivalent dose and 10 times the epirubicin-equivalent dose.

Thus it is recommended that Cardioxane is given at a dose of 500 mg/m² when the commonly used dosage schedule for doxorubicin of 50 mg/m² is employed or 600 mg/m² when the commonly used dosage schedule for epirubicin of 60 mg/m² is employed.

Paediatric population

The safety and efficacy of Cardioxane in children aged 0 to 18 years have not been established. Currently available data are described in section 4.3, 4.4, 4.8, 5.1 and 5.2.

Renal impairment

In patients with moderate to severe renal impairment (creatinine clearance < 40 ml/min) the dexrazoxane dose should be reduced by 50% (see section 4.4).

Hepatic impairment

The dosage ratio should be kept, i.e. if the anthracycline dose is reduced the dexrazoxane dose should be reduced accordingly.

Method of administration

Intravenous use

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Cardioxane is contraindicated in children aged 0 to 18 years who are planned to receive a cumulative dose of less than 300 mg/m² of doxorubicin or the equivalent cumulative dose of another anthracycline (see sections 4.4 and 4.8).

Cardioxane is also contraindicated in the following circumstances:

- Hypersensitivity to dexrazoxane
- Breast-feeding (see section 4.6)
- Concomitant vaccination with yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

Myelosuppression

Myelosuppressive effects that may be additive to those of chemotherapy were reported with Cardioxane (see section 4.8). Cell counts at nadir may be lower in patients treated with dexrazoxane. Haematological monitoring is thus necessary. Leucopenia and thrombocytopenia generally reverse quickly upon cessation of treatment with Cardioxane.

At higher doses of chemotherapy, where the Cardioxane dose exceeds 1000 mg/m², myelosuppression may increase significantly.

Second primary malignancies

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.

Oncology patients have an increased risk of second primary malignancies, regardless of treatment. Patients who have received cancer therapy also have an increased risk of second primary malignancy.

Acute Myeloid Leukaemia (AML) has been reported uncommonly in adult breast cancer patients post-marketing (see section 4.8).

In paediatric patients, second primary malignancies, including acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), have been reported in clinical trials in both dexrazoxane and control groups. Although second primary malignancies were numerically higher in the dexrazoxane arm, there was no statistical difference between groups. Overall, the rates of second primary malignancies in the available paediatric studies in the dexrazoxane group are similar to rates determined for relevant populations in other studies (historical data). However, the long term effect of dexrazoxane on second primary malignancies is not known and cannot be estimated from the available data. In clinical trials, second primary malignancies, in particular 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) (see section 4.8).

Interference with chemotherapy

Since both dexrazoxane and anthracyclines are topoisomerase inhibitors, it has been suggested that dexrazoxane may interfere with the anti-tumour efficacy of anthracyclines based on mechanism of action. However, in most adult studies no significant difference has been identified in response rate and overall survival between dexrazoxane and control groups. A significant decrease in tumour response rate was reported in one study of advanced breast cancer patients treated with doxorubicin and dexrazoxane compared to patients treated with doxorubicin and placebo. In this study placebo response rate was considered to be high (60.5%), which

may be a contributing factor to the observed difference in response rate. Despite the difference in response rates, there was no significant difference in time to progression or overall survival between patients that had received either dexrazoxane or placebo in this study.

No paediatric study has reported a difference in oncological outcome (event free survival) between groups treated with dexrazoxane and those treated with anthracycline alone.

Patients with renal impairment

Clearance of dexrazoxane and its active metabolites may be reduced in patients with decreased creatinine clearance (see Section 4.2).

Liver disorders

Since liver dysfunction was occasionally observed in patients treated with Cardioxane (see section 4.8), it is recommended that routine liver function tests be performed before and during administration of dexrazoxane in patients with known liver function disorders.

Patients with cardiac disorders

Standard cardiac monitoring associated with doxorubicin or epirubicin treatment should be continued.

There are no data that support the use of dexrazoxane in patients with myocardial infarction within the past 12 months, pre-existing heart failure (including clinical heart failure secondary to anthracycline treatment), uncontrolled angina or symptomatic valvular heart disease.

Thromboembolism

Combination of dexrazoxane with chemotherapy may lead to an increased risk of thromboembolism (see section 4.8).

Women of child-bearing potential / Contraception in males and females

Since dexrazoxane is a cytotoxic agent, sexually active men and women should use effective contraception during treatment. Women and men should continue using effective methods of contraception for at least 6 months after cessation of treatment with dexrazoxane (see section 4.6).

Geriatric patients (age 65 years or above)

There are no clinical trials comparing the efficacy or safety of dexrazoxane in geriatric patients to that in younger patients. However, in general, caution is required when treating elderly patients due to their greater use of other medicinal products, higher rates of concomitant diseases and possible reduced hepatic, renal or cardiac function.

Anaphylactic reaction

Anaphylactic reaction including angioedema, skin reactions, bronchospasm, respiratory distress, hypotension and loss of consciousness have been observed in patients treated with Cardioxane and anthracyclines (see section 4.8). Previous history of allergy to dexrazoxane should be carefully considered prior to administration (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Cardioxane is excreted unchanged via the kidney, as well as metabolized by dihydropyrimidine amidohydrolase (DHPase) in the liver and kidney to ring-opened metabolites. Co-administration of doxorubicin (50 to 60 mg/m²) or epirubicin (60 to 100 mg/m²) did not affect Cardioxane pharmacokinetics significantly.

In studies, Cardioxane did not affect the pharmacokinetics of doxorubicin. There is limited evidence from studies that suggests that epirubicin clearance may be increased when dexrazoxane is pre-administered, this occurred at high doses of epirubicin (120-135 mg/m²).

Cardioxane may increase haematological toxicity induced by chemotherapy or radiation, requiring careful monitoring of haematological parameters during the first two treatment cycles (see section 4.4).

Cardioxane should not be mixed with any other medicinal products during infusion.

Concomitant use contraindicated:

Yellow fever vaccine: Risk of fatal generalised vaccine disease (see section 4.3).

Concomitant use not recommended:

Other live attenuated vaccines: risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).

Phenytoin: cytotoxic agents may reduce the absorption of phenytoin leading to an exacerbation of convulsions. Dexrazoxane is not recommended in combination with phenytoin.

Concomitant use to assess carefully:

Ciclosporin, tacrolimus: Excessive immunosuppression with risk of lymphoproliferative disease.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential/contraception in males and females

Both sexually active men and women should use effective methods of contraception during treatment. For women and men the contraception should be continued for at least 6 months after cessation of treatment with Cardioxane (see section 4.4).

Pregnancy

There are no adequate data from the use of dexrazoxane in pregnant women. Animal studies showed embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Cardioxane is used with anthracyclines known to have cytotoxic, mutagenic and embryotoxic properties. Cardioxane should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no animal studies on the transfer of the active substance and/or its metabolites into milk. It is unknown whether dexrazoxane and/or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in infants exposed to Cardioxane, breast-feeding is contraindicated during Cardioxane treatment (see section 4.3).

Fertility

The effect of Cardioxane on the fertility of humans has not been studied.

There are limited fertility data from animal studies available, but testicular changes were observed in rats and dogs following repeat dosing (see Section 5.3).

4.7 Effects on ability to drive and use machines

Cardioxane has moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Cardioxane.

4.8 Undesirable effects

Summary of the safety profile

Cardioxane is administered together with anthracycline chemotherapy and, consequently, the relative contributions of anthracycline and Cardioxane to the adverse reaction profile may be unclear. The most common adverse reactions are haematological and gastroenterological reactions, primarily anaemia, leukopenia, nausea, vomiting and stomatitis, as well as asthenia and alopecia. Myelosuppressive effects of Cardioxane may be additive to those of chemotherapy (see section 4.4).

Tabulated list of adverse reactions

The following table includes reactions from clinical trials and from post-marketing use. Due to the spontaneous nature of post-marketing reporting, such events are listed with frequency “not known” if they were not already identified as reactions from clinical trials.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); not known (cannot be estimated from the available data).

Table 1

Infections and infestations	
Uncommon	Infection, sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Acute myeloid leukaemia
Blood and lymphatic system disorders	
Very common	Anaemia, leukopenia
Common	Neutropenia, thrombocytopenia, febrile neutropenia, granulocytopenia, febrile bone marrow aplasia, white blood cell count decreased
Uncommon	Eosinophil count increased, neutrophil count increased, platelet count increased, white blood cell count increased, lymphocyte count decreased, monocyte count decreased
Immune system disorders	
Not known	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	
Common	Anorexia
Nervous system disorders	
Common	Paraesthesia, dizziness, headache, peripheral neuropathy
Uncommon	Syncope
Ear and labyrinth disorders	
Uncommon	Vertigo, ear infection
Cardiac disorders	
Common	Ejection fraction decreased, tachycardia
Vascular disorders	

Common	Phlebitis
Uncommon	Venous thrombosis, lymphoedema
Not known	Embolicism
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough, pharyngitis, respiratory tract infections
Not known	Pulmonary embolism
Gastrointestinal disorders	
Very common	Nausea, vomiting, stomatitis
Common	Diarrhoea, constipation, abdominal pain, dyspepsia
Uncommon	Gingivitis, oral candidiasis
Hepatobiliary disorders	
Common	Transaminases increased
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Nail disorder, erythema
Uncommon	Cellulitis
General disorders and administration site conditions	
Very common	Asthenia
Common	Mucosal inflammation, pyrexia, fatigue, malaise, injection site reaction (including pain, swelling, burning sensation, erythema, pruritus, thrombosis), oedema
Uncommon	Thirst

Clinical trial data

The above table shows adverse reactions reported in clinical studies and having a reasonable possibility of a causal relationship with Cardioxane. These data are derived from clinical trials in cancer patients where Cardioxane was used in combination with anthracycline-based chemotherapy, and where in some cases a control group of patients receiving chemotherapy alone can be referred to.

Patients receiving chemotherapy and Cardioxane (n=375):

- Of these 76% were treated for breast cancer and 24% for a variety of advanced cancers.
- Cardioxane treatment: a mean dose of 1010 mg/m² (median: 1000 mg/m²) in combination with doxorubicin, and a mean dose of 941 mg/m² (median: 997 mg/m²) in combination with epirubicin.
- Chemotherapy treatment received by patients treated for breast cancer: 45% combination therapy with doxorubicin 50 mg/m² (mainly with 5-fluorouracil and cyclophosphamide): 17% with epirubicin alone; 14% combination therapy with epirubicin 60 or 90 mg/m² (mainly with 5-fluorouracil and cyclophosphamide).

Patients receiving chemotherapy alone (n=157)

- All were treated for breast cancer
- Chemotherapy treatment received: 43% single agent epirubicin 120 mg/m²; 33% combination therapy with 50 mg/m² doxorubicin (mainly with 5-fluorouracil and cyclophosphamide); 24% combination therapy with epirubicin at 60 or 90 mg/m² (mainly with 5-fluorouracil and cyclophosphamide).

Description of selected adverse drug reactions

Second primary malignancies

AML has been reported uncommonly in adult breast cancer patients post-marketing.

Safety profile at maximum tolerated dose

Dexrazoxane's maximum tolerated dose (MTD) when given as monotherapy by short infusion every three weeks for cardioprotection has not been specifically studied. In studies of dexrazoxane as a cytotoxic, its MTD is shown to be dependent on posology and dosing schedule, and varies from 3750 mg/m² when short infusions are given in divided doses over 3 days to 7420 mg/m² when given weekly for 4 weeks, with myelosuppression and abnormal liver function tests becoming dose-limiting. The MTD is lower in patients who have been heavily pre-treated with chemotherapy, and those with pre-existing immunosuppression (e.g. AIDS).

The following are adverse reactions reported when Cardioxane was given at doses around the MTD: neutropenia, thrombocytopenia, nausea, vomiting, and increase in hepatic parameters. Other toxic effects were malaise, low grade fever, increased urinary clearance of iron and zinc, anaemia, abnormal blood clotting, transient elevation of serum triglyceride and amylase levels, and a transient decrease in serum calcium level.

Paediatric population

The safety experience in children is based primarily on literature reports of clinical trials in acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and osteosarcoma, and post-marketing data.

In paediatric patients, second primary malignancies, including acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), have been reported in clinical trials in both dexrazoxane and control groups. Although second primary malignancies were numerically higher in the dexrazoxane arms, there was with no statistical difference between groups. In addition, the long term effect of dexrazoxane on secondary primary malignancies is not known (cannot be estimated from the available data) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The signs and symptoms of overdose are likely to consist of leucopenia, thrombocytopenia, nausea, vomiting, diarrhoea, skin reactions and alopecia. There is no specific antidote and symptomatic treatment should be provided.

Management should include prophylaxis and treatment of infections, fluid regulation, and maintenance of nutrition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V03AF02

Mechanism of action

The exact mechanism by which dexrazoxane exerts its cardioprotective effect has not been fully elucidated, however based on the available evidence the following mechanism has been suggested. The dose-dependent cardiotoxicity observed during anthracycline administration is due to anthracycline-induced iron-dependent free radical oxidative stress on the relatively unprotected cardiac muscle. Dexrazoxane, an analogue of EDTA (ethylene diamine tetra-acetic acid), is hydrolysed in cardiac cells to the ring-opened product ICRF-198. Both dexrazoxane (ICRF-187) and ICRF-198 are capable of chelating metal ions. It is generally thought that they can provide cardioprotection by scavenging metal ions thus preventing the Fe³⁺-anthracycline complex from redox cycling and forming reactive radicals.

Clinical efficacy and safety

The evidence from clinical trials to date suggests increasing cardioprotective benefit from dexrazoxane as the cumulative anthracycline dose is increased.

Dexrazoxane does not protect against non-cardiac toxicities induced by anthracyclines.

The majority of controlled clinical studies were performed in patients with advanced breast cancer and employed a dosing ratio of dexrazoxane:doxorubicin of 20:1 or 10:1. In two clinical studies that used the higher dose ratio (one in breast cancer and one in small cell lung cancer) a higher rate of death was reported in the groups treated with dexrazoxane plus chemotherapy compared to those treated with chemotherapy alone or with placebo. The dose ratio was subsequently reduced to 10:1 in both studies, and no significant differences in survival were reported in patients treated at the lower dose ratio. However, a number of studies that used the higher dose ratio throughout have not reported any difference in survival.

Paediatric Population:

There are limited data on efficacy in children. Data are mainly derived from COG (Children's Oncology Group) studies, published in BL Asselin *et al*: J. Clin. Oncol. 2016 and CL Schwartz *et al* *Pediatr. Blood Cancer* 2016.

Study P9404 (BL Asselin *et al*: J. Clin. Oncol. 2016) evaluated the cardioprotective efficacy, and safety of dexrazoxane added to chemotherapy that included a cumulative doxorubicin dose of 360 mg/m² to treat children and adolescents with newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL) or lymphoblastic non-Hodgkin lymphoma (L-NHL). Between June 1996 and September 2001, patients were randomised to receive doxorubicin treatment with (n=273) or without (n=264) dexrazoxane (dexrazoxane: doxorubicin ratio 10:1). Dexrazoxane was given as a bolus infusion immediately before every dose of doxorubicin. Cardiac effects were assessed by echocardiographic measurements of left ventricular function and structure.

Baseline characteristics of the overall study population were as follows: median age at diagnosis 9.2 years, male (75.8%), White (66%), T-ALL (67%). The treatment used was modified from study protocol DFCI ALL-87-01 with or without high-dose methotrexate and all patients received cranial radiation.

Heart failure was not reported among patients at any time during treatment or follow-up. Of the five patients in whom grade 3 or 4 cardiac toxicity occurred while receiving therapy; two had arrhythmias (n = 1 in the dexrazoxane group), and three had decreased LV fractional shortening (all were in the no-dexrazoxane group). All five received high-dose methotrexate and had a serious infection when the cardiac toxicity occurred. All patients recovered and completed chemotherapy, including doxorubicin. cTnT levels at both baseline and during treatment were available for 160 patients. The probability of having elevated cTnT was lower in the dexrazoxane group (odds ratio, 0.23; 95% CI, 0.05 to 1.11; p = 0.067).

At baseline, mean z scores for LV fractional shortening and LV thickness-to-dimension ratio were similar between treatment groups. The mean z score for LV wall thickness at baseline in the dexrazoxane-treated group was significantly lower than in the no-dexrazoxane group. The LV wall thickness was worse after treatment in the no-dexrazoxane treatment group than it was in the dexrazoxane-treated group. After doxorubicin treatment, mean z scores were lower than age-expected norms for all children, but were not significantly different between groups; the mean score was always closer to normal for the dexrazoxane group. The mean z scores for left

ventricular fractional shortening, LV wall thickness, and LV thickness-to-dimension ratio at three years in dexrazoxane treated children were not significantly different from the scores for healthy children; whereas in the no-dexrazoxane group these z scores all remained significantly reduced compared to healthy children. The mean left ventricular fractional shortening, wall thickness, and thickness-to-dimension ratio z scores measured 3 years after diagnosis were worse in the doxorubicin-alone group (n = 55 per group; $P \leq 0.01$ for all comparisons).

The 5-year event-free survival (with standard error) did not differ between groups: 76.7% (2.7%) for the dexrazoxane group versus 76.0% (2.7%) for the doxorubicin-only group ($p = 0.9$) (see also sections 4.2, 4.3, 4.4 and 4.8). The frequencies of severe grade 3 or 4 haematologic toxicity, infection, central nervous system events, and toxic deaths were similar in both groups.

In a non-randomised study (P9754, CL Schwartz *et al* *Pediatr. Blood Cancer* 2016) in patients with non-metastatic osteosarcoma (median age 13 years, range 3-30 years) where all patients receiving doxorubicin (450-600 mg/m²) also received dexrazoxane (dexrazoxane: doxorubicin ratio 10:1) (242 patients exposed to at least 450 mg/m² doxorubicin and 101 exposed to 600 mg/m²), Grade 1 or 2 left ventricular dysfunction occurred in five patients, and was transient in at least four of these. In two of these patients, doxorubicin was subsequently discontinued. No grade 3, 4 or 5 cardiomyopathy (ventricular dysfunction) was observed. One additional patient had grade 3 serum cTnT elevation with 600 mg/m² doxorubicin without documented myocardial dysfunction. Left ventricular fractional shortening values from 104 evaluable patients were converted to z-scores (FSZ) to review change in cardiac function since time of enrolment. It was found that FSZ decreased in a statistically significant fashion with increasing time, with that change being -0.017 ± 0.009 of a standardised unit (z-score of 1) per week (estimated annual change of 0.9 FSZ units). Assignment to standard therapy (450 mg/m² doxorubicin) or intensification (600 mg/m² doxorubicin) was unrelated to change in FSZ. In terms of clinical cardiotoxicity, biomarker measures and FSZ analysis, the risk of acute cardiomyopathy was low, given the cumulative doses of 450 mg/m² to 600 mg/m² of doxorubicin (see also sections 4.2, 4.3, 4.4 and 4.8).

5.2 Pharmacokinetic properties

After intravenous administration to cancer patients, serum kinetics of dexrazoxane generally follow an open two-compartment model with first-order elimination. The maximum plasma concentration observed after a 12-15 minute infusion of 1000 mg/m² is around 80 µg/ml with area under the plasma concentration-time curve (AUC) of 130 ± 27 mg.h/l. The plasma concentrations declined thereafter with an average half-life value of 2.2 ± 0.42 hours. The total body clearance of dexrazoxane in adults is estimated at 14.4 ± 2.8 l/h.

Distribution

The apparent volume of distribution is 44.0 ± 3.9 l, suggesting that dexrazoxane distributes mainly in the total body water. Plasma protein binding of dexrazoxane is

low (2%) and it does not penetrate into the cerebrospinal fluid to a clinically significant extent.

Biotransformation and metabolism

Cardioxane and its metabolites were detected in the plasma and urine of animals and man.

Elimination

Urinary excretion plays an important role in the elimination of dexrazoxane. The total urinary excretion of unchanged dexrazoxane is in the order of 40%.

Special populations

Paediatric patients

The very limited pharmacokinetic data in children suggests that although absolute values of clearance are higher, values normalised for body surface area are not significantly different from those of adults.

Geriatric patients

No studies have been conducted in the elderly and dexrazoxane. Clearance may be reduced in elderly patients and patients with low creatinine clearance.

Hepatic impairment

No studies have been conducted in subjects with hepatic impairment.

Renal impairment

Compared with normal subjects (creatinine clearance (CLCR) >80 ml/min), exposure was 2-fold greater in subjects with moderate (CLCR of 30 to 50 ml/min) to severe (CLCR <30 ml/min) renal impairment. Modelling suggested that equivalent exposure (AUC_{0-inf}) could be achieved if dosing were reduced by 50% in subjects with CLCR less than 40 ml/min compared with control subjects (CLCR >80 ml/min).

5.3 Preclinical safety data

Repeat dose toxicity

Preclinical studies indicate that, with repeated dexrazoxane administration, the primary target organs are those of rapid cell division: bone marrow, lymphoid tissue, testes and gastrointestinal mucosa. Dexrazoxane administration has been associated with testicular atrophy in rats starting at intravenous dose levels of 25 mg/kg and at a dose level of 20 mg/kg/week in dogs.

The Cardioxane dosing schedule is a primary factor in the degree of tissue toxicity produced. A single high dose is better tolerated than the same dose administered several times a day.

Mutagenicity

Dexrazoxane has been shown to possess mutagenic and genotoxic activity in both in vitro and in vivo studies.

Carcinogenicity

The carcinogenic potential of dexrazoxane has not been investigated. However prolonged administration of high doses of razoxane, the racemic mixture of which dexrazoxane is the S (+)-enantiomer, has been associated with the development of hematopoietic neoplasms in female mice, lymphocytic neoplasms in female mice and uterine adenocarcinomas in female rats.

Reproductive toxicity- teratogenicity

There are limited fertility data from animal studies available, but testicular changes were observed in rats and dogs following repeat dosing.

Animal reproductive studies reveal that razoxane is embryotoxic in mice, rats and rabbits and also teratogenic in rats and mice (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Before opening:

3 years

After reconstitution and dilution:

Chemical and physical in-use stability of reconstituted and subsequently diluted CARDIOXANE is 4 hours at 25°C.

From a microbiological point of view, reconstituted and subsequently diluted CARDIOXANE should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user, and should not be longer than 4 hours at 2°C to 8°C (in the refrigerator) with protection from light.

6.4 Special precautions for storage

Before opening: Do not store above 25°C. In order to protect from light store in the original package.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vials (Type I brown glass), containing 500 mg of powder, closed with a stopper (chlorobutyl rubber) and a cap (aluminium) with a flip-off component (polypropylene). The product is further enclosed in an outer carton. It is supplied in packs of 1 and 4 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Recommendations for safe handling

Prescribers should refer to national or recognised guidelines on handling cytotoxic agents when using Cardioxane. Reconstitution should only be carried out by trained staff in a cytotoxic designated area. The preparation should not be handled by pregnant staff.

Use of gloves and other protective clothing to prevent skin contact is recommended. Skin reactions have been reported following contact with Cardioxane. If Cardioxane powder or solution comes into contact with the skin or mucosal surfaces, the affected area should immediately be rinsed thoroughly with water.

Preparation for intravenous administration

Reconstitution of Cardioxane

For reconstitution the contents of each vial should be dissolved in 25 ml 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. This solution should be further diluted before administration to the patient.

Dilution of Cardioxane

To avoid the risk of thrombophlebitis at the injection site, Cardioxane should be diluted prior to infusion with one of the solutions mentioned in the table below. Preferably solutions with a higher pH should be used. The final volume is proportional to the number of vials of Cardioxane used and the amount of infusion fluid for dilution, which can be between 25 ml and 100 ml per vial.

The table below summarises the final volume and the approximate pH of reconstituted and diluted product for one vial and four vials of Cardioxane. The minimum and maximum volumes of infusion fluids to be used per vial are shown below.

Infusion fluid used for dilution	Volume of fluid used to dilute 1 vial of reconstituted Cardioxane	Final volume from 1 vial	Final volume from 4 vials	pH (approximate)
Ringer lactate	25 ml	50 ml	200 ml	2.2
	100 ml	125 ml	500 ml	3.3
0.16 M sodium lactate*	25 ml	50 ml	200 ml	2.9
	100 ml	125 ml	500 ml	4.2

* Sodium lactate 11.2% should be diluted by a factor of 6 to reach a concentration of 0.16 M.

The use of larger dilution volumes (with a maximum of 100 ml of additional infusion fluid per 25 ml reconstituted Cardioxane) is usually recommended to increase the pH of the solution. Smaller dilution volumes (with a minimum of 25 ml of additional infusion fluid per 25 ml reconstituted Cardioxane) can be used if needed, based on the haemodynamic status of the patient.

Cardioxane is for single use only. Reconstituted and subsequently diluted product should be used immediately or within 4 hours if stored between 2°C and 8°C.

Parenteral drug products should be inspected visually for particulate matter whenever the solution and container permit. Cardioxane is normally a colourless to yellow solution immediately on reconstitution, but some variability in colour may be observed over time, which does not indicate loss of activity if the product has been stored as recommended. It is however recommended to dispose of the product if the colour immediately on reconstitution is not colourless to yellow.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Adequate care and precautions should be taken in the disposal of items used to reconstitute and dilute Cardioxane.

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8 MARKETING AUTHORISATION NUMBER(S)

PL 19635/0007

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

Date of first authorisation: 7 July 2006

Date of the latest renewal: 9 October 2015

10 DATE OF REVISION OF THE TEXT

31/01/2024