

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Cardioxane 500mg Powder for Concentrate for Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cardioxane contains 500 mg lyophilized dexrazoxane, as its hydrochloric salt.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for Concentrate for Solution for Infusion.

Sterile, pyrogen-free, white to off-white, lyophilized powder for solution for infusion.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic adult breast cancer patients who have received a prior cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> 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/m<sup>2</sup> when the commonly used dosage schedule for doxorubicin of 50 mg/m<sup>2</sup> is employed or 600 mg/m<sup>2</sup> when the commonly used dosage schedule for epirubicin of 60 mg/m<sup>2</sup> is employed.

#### *Paediatric population*

Cardioxane is contraindicated in children and adolescents up to 18 years of age (see section 4.3).

#### *Renal impairment*

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

#### *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

- Children and adolescents up to 18 years of age (see sections 4.4 and 4.8)
- Patients who are hypersensitive to dexrazoxane
- Breast-feeding (see section 4.6)

### 4.4 Special warnings and precautions for use

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/m<sup>2</sup>, myelosuppression may increase significantly.

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 regimes including several cytotoxics (e.g. etoposide, doxorubicin, cyclophosphamide) (see section 4.8).

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

In some studies, a higher incidence of death has been observed in the groups treated with dexrazoxane plus chemotherapy compared to those treated with chemotherapy alone. The possibility that dexrazoxane was a contributing factor to the imbalance cannot be ruled out (see section 5.1).

A significant decrease in tumour response rate has been reported in one study in advanced breast cancer patients treated with doxorubicin and dexrazoxane compared to patients treated with doxorubicin and placebo. Since both dexrazoxane and doxorubicin are topoisomerase inhibitors, it is possible that dexrazoxane may interfere with the anti-tumour efficacy of doxorubicin. Use of dexrazoxane in combination with adjuvant breast cancer therapy or chemotherapy intended as curative is therefore not recommended.

Clearance of dexrazoxane and its active metabolites may be reduced in patients with decreased creatinine clearance.

Liver dysfunction was occasionally observed in patients treated with Cardioxane (see section 4.8).

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.

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

Since dexrazoxane is a cytotoxic agent, sexually active men should continue using effective methods of contraception for at least 3 months after cessation of treatment with dexrazoxane (see section 4.6).

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 or razoxane should be carefully considered prior to administration.

## 4.5 Interaction with other medicinal products and other forms of interaction

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).

Interaction studies with dexrazoxane are limited. Effects on CYP450 enzymes or drug transporters have not been studied.

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

## 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 men the contraception should be continued for at least 3 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 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, mothers should discontinue breast-feeding during Cardioxane therapy (see section 4.3).

### Fertility

The effects of Cardioxane on the fertility of humans and animals have not been studied.

## 4.7 Effects on 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

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). An increased risk of the development of second primary malignancies, particularly AML, has been reported.

### 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

<b>Infections and infestations</b>	
Uncommon	Infection, sepsis
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	
Uncommon	Acute myeloid leukaemia
<b>Blood and lymphatic system disorders</b>	
Very common	Anaemia, leukopenia
Common	Neutropenia, thrombocytopenia, febrile neutropenia, granulocytopenia
Uncommon	Febrile bone marrow aplasia, eosinophil count increased, neutrophil count increased, platelet count increased, white blood cell count increased, lymphocyte count decreased, monocyte count decreased
<b>Immune system disorders</b>	
Not known	Anaphylactic reaction, hypersensitivity
<b>Metabolism and nutrition disorders</b>	
Common	Anorexia
<b>Nervous system disorders</b>	
Common	Paraesthesia, dizziness, headache, peripheral neuropathy
Uncommon	Syncope
<b>Eye disorders</b>	
Common	Conjunctivitis
<b>Ear and labyrinth disorders</b>	
Uncommon	Vertigo, ear infection
<b>Cardiac disorders</b>	
Common	Ejection fraction decreased, tachycardia
<b>Vascular disorders</b>	
Common	Phlebitis
Uncommon	Venous thrombosis, lymphoedema
Not known	Embolism
<b>Respiratory, thoracic and mediastinal disorders</b>	
Common	Dyspnoea, cough, pharyngitis
Uncommon	Respiratory tract infection
Not known	Pulmonary embolism
<b>Gastrointestinal disorders</b>	
Very common	Nausea, vomiting, stomatitis
Common	Diarrhoea, constipation, abdominal pain, dyspepsia
Uncommon	Gingivitis, oral candidiasis
<b>Hepatobiliary disorders</b>	
Common	Transaminases increased
<b>Skin and subcutaneous tissue disorders</b>	
Very common	Alopecia
Common	Nail disorder, erythema
<b>General disorders and administration site conditions</b>	
Very common	Asthenia
Common	Mucosal inflammation, pyrexia, fatigue, malaise, injection site reaction (including pain, swelling, burning sensation, erythema, pruritus, thrombosis)
Uncommon	Oedema, 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/m<sup>2</sup> (median: 1000 mg/m<sup>2</sup>) in combination with doxorubicin, and a mean dose of 941 mg/m<sup>2</sup> (median: 997 mg/m<sup>2</sup>) in combination with epirubicin.
- Chemotherapy treatment received by patients treated for breast cancer: 45% combination therapy with doxorubicin 50 mg/m<sup>2</sup> (mainly with 5-fluorouracil and cyclophosphamide); 17% with epirubicin alone; 14% combination therapy with epirubicin 60 or 90 mg/m<sup>2</sup> (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/m<sup>2</sup>; 33% combination therapy with 50 mg/m<sup>2</sup> doxorubicin (mainly with 5-fluorouracil and cyclophosphamide); 24% combination therapy with epirubicin at 60 or 90 mg/m<sup>2</sup> (mainly with 5-fluorouracil and cyclophosphamide).

#### Second primary malignancies

Secondary acute myeloid leukaemia (AML) / myelodysplastic syndrome (MDS) has been observed in paediatric patients with Hodgkin's disease or acute lymphoblastic leukaemia receiving dexrazoxane in combination with chemotherapy (see section 4.4). 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/m<sup>2</sup> when short infusions are given in divided doses over 3 days to 7420 mg/m<sup>2</sup> 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, anemia, abnormal blood clotting, transient elevation of serum triglyceride and amylase levels, and a transient decrease in serum calcium level.

## **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

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 Fe<sup>3+</sup>-anthracycline complex from redox cycling and forming reactive radicals.

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. Data from adults treated in 8 controlled randomised clinical studies have been reviewed, 780 patients received dexrazoxane plus chemotherapy and 789 received chemotherapy alone. The rate of death on study was higher with the combination dexrazoxane plus chemotherapy (5.0%) compared to chemotherapy alone (3.4%). The difference was not statistically significant and no consistent cause was apparent, however a contribution of dexrazoxane to the difference cannot be ruled out.

## 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/m<sup>2</sup> is around 80 µg/ml with area under the plasma concentration-time curve (AUC) of 130 ± 15 mg.h/l. The plasma concentrations declined thereafter with an average half-life value of 2.2 ± 1.2 hours. The apparent volume of distribution is 44.0 ± 3.9 l, suggesting that dexrazoxane distributes mainly in the total body water. The total body clearance of dexrazoxane in adults is estimated at 14.4 ± 1.6l/h. Cardioxane and its metabolites were detected in the plasma and urine of animals and man. The majority of the administered dose is eliminated in urine mainly as unchanged dexrazoxane.

The total urinary excretion of unchanged dexrazoxane is in the order of 40%. Plasma protein binding of dexrazoxane is low (2%) and it does not penetrate into the cerebrospinal fluid to a clinically significant extent. Active substance clearance may be reduced in elderly patients and patients with low creatinine clearance. There is limited data on pharmacokinetic interactions with chemotherapeutic agents other than doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil and paclitaxel. No studies were conducted in the elderly and subjects with hepatic or renal impairment.

## 5.3 Preclinical safety data

Preclinical studies indicate that with repeated dexrazoxane administration, the primary target organs are those of rapid cell division: bone marrow, lymphoid tissue, testes and gastro-intestinal mucosa. 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.

Dexrazoxane has been shown to possess mutagenic activity. 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 secondary malignancies (primarily acute myeloid leukaemia). Animal reproduction studies reveal that razoxane is embryotoxic to mice, rats and rabbits and also teratogenic to rats and mice, although a different dosing schedule was used compared to that used in man.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Not applicable

### 6.2 Incompatibilities

Incompatibilities with other medicinal products or materials are not known. However Cardioxane should not be mixed with other medicinal products during infusion, other than the diluents 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.

**6.5 Nature and contents of container**

Vials (Type I brown glass), containing 500 mg of powder, closed with a chlorobutyl rubber stopper and an aluminium cap with pre-cut strip. 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

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 25ml 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 25ml 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 obtained from 1 vial	Final volume obtained from 4 vials	pH (approximate)
Ringer lactate	25 ml	50 ml	200 ml	2,2
	100 ml	125 ml	500 ml	3,3

0.16M 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 0.16M

The use of larger dilution volumes (with a maximum of 100 ml of additional infusion fluid per 25ml 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 25ml 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 solution should be discarded in accordance with local requirements. Adequate care and precautions should be taken in the disposal of items used to reconstitute and dilute Cardioxane.

**7 MARKETING AUTHORISATION HOLDER**

Novartis Pharmaceuticals UK Ltd  
Frimley Business Park  
Frimley, Camberley  
Surrey GU16 7SR  
United Kingdom

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