NOVARTIS

Drug Regulatory Affairs

CARDIOXANE®

(dexrazoxane)

500 mg powder for solution for infusion

Reference labelling document for prescribers

NOTICE

The reference labelling document for prescribers is based on European Mutual Recognition Procedure Summary of Product Characteristics (EU MRP SmPC). As there is no Core Data Sheet for Cardioxane, the EU MRP SmPC is used as a vehicle for implementing safety labelling changes globally.

Author(s): Sandra Jullian

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1. NAME OF THE MEDICINAL PRODUCT

CARDIOXANE® 500mg, powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dexrazoxane 500.00mg as its hydrochloride salt.
For a vial of powder.

For 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

Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic cancer patients after previous anthracycline containing treatment.

4.2 Posology and method of administration

Cardioxane is administered by a short intravenous infusion (15 minutes), approximately 30 minutes prior to anthracycline administration at a dose equal to 20 times the doxorubicin-equivalent dose and 10 times the epirubicin-equivalent dose.

Thus it is recommended that Cardioxane is given at a dose of 1000 mg/m^2 when the commonly used dosage schedule for doxorubicin of 50 mg/m^2 or epirubicin 100 mg/m^2 is employed.

Renal impairment: In patients with moderate to severe renal dysfunction (creatinine clearance <40ml/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.

Paediatric patients: The experience in children is limited (see section 4.4, 5.1 and 5.2).

4.3 Contraindications

Hypersensitivity to dexrazoxane.
Lactation.

4.4 Special warnings and special precautions for use

Myelosuppressive effects that may be additive to those of chemotherapy were reported with Cardioxane. 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 1000mg/m^2, myelosuppression may increase significantly.

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.

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

There is limited data on the use of dexrazoxane in combination with adjuvant therapy or chemotherapy intended as curative, therefore the effect on anti-tumour efficacy in these populations is unknown (see section 5.1).

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.

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.

In paediatric patients with Hodgkin lymphoma receiving chemotherapy with several cytotoxic drugs (e.g etoposide, doxorubicin, cyclophosphamide) second primary malignancies have been reported. Since dexrazoxane has topoisomerase II inhibitor activity, combination of dexrazoxane with other topoisomerase II inhibitor agents, may potentially increase the risk of second primary malignancy in this patient population [2,3].

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 Pregnancy and lactation

There are no adequate data from the use of dexrazoxane in pregnant women. Animal studies showed embryotoxic and teratogenic effects (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Cardioxane should not be used during pregnancy unless clearly necessary. 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).

There are no animal studies on the transfer of the active substance and/or its metabolites into milk. It is not known whether Cardioxane is 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).

4.7 Effects on ability to drive and use machines

There are no data on the effect of Cardioxane on the ability to drive and use machines.

4.8 Undesirable effects

At the doses recommended for cardioprotection, Cardioxane, in combination with anthracyclines, did not increase the incidence or severity of clinical signs of toxicity of anthracycline based regimens, with the exception of haematological effects that are reported more frequently; most often, these are neutropenia that can be severe and sometimes serious. Very rarely, they can be associated with thrombocytopenia and/or anemia, or even bone marrow aplasia. The relative contribution of Cardioxane and chemotherapeutic agents is unclear.

The most common adverse events (those occurring in more than 10% of patients) reported in clinical studies with anthracycline based chemotherapy used alone or in association with Cardioxane are gastrointestinal disorders, blood and lymphatic system disorders, general disorders and administration site conditions and skin and subcutaneous tissue disorders (see adverse events table below).

Other Undesirable Effects reported during the use of Cardioxane

Infections: upper respiratory tract and pulmonary infections, septicaemia.

Immune system disorders: Anaphylactic reaction [1], hypersensitivity.

Anaphylactic reaction including, but not limited to, angioedema, facial oedema, nasal oedema, laryngeal oedema, generalised pruritus, macular erythema, dyspnoea, cough, bronchospasm, hypotension, status asthmaticus, hypoxia, respiratory distress/discomfort, stridor and shock/loss of consciousness have been observed in some patients treated with Cardioxane and anthracyclines. Allergic predispositions to dexrazoxane, razoxane and/or anthracyclines should be carefully considered prior to administration [1].

Vascular disorders: venous thromboembolic disease (phlebitis, pulmonary embolism).

General disorders and administration site conditions: Administration/injection site reactions (pain, swelling/oedema, burning sensation, erythema, pruritus, skin necrosis and extravasation) [1] and phlebitis.

Adverse Events observed in Clinical Studies

The following data (see table below) are the adverse events observed in greater than 1% of the 375 patients receiving chemotherapy in combination with Cardioxane during clinical studies and in 157

patients receiving chemotherapy alone. In the combination arm the adverse events are considered related to either anthracycline or Cardioxane and not specifically to Cardioxane.

Patients and treatments

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).
- Chemotherapy treatment of patients with advanced cancers other than breast cancer: 18% single or combination therapy with doxorubicin 50 mg/m²; 4% single agent doxorubicin 100 mg/m² + GCSF; 2% complex treatment for non Hodgkins lymphoma including epirubicin, mitoxantrone.

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).

Common Adverse Events in >1% of Patients Receiving Either Chemotherapy Alone or in Combination with Cardioxane

Adverse Events	**Chemotherapy and CARDIOXANE** n = 375	**Chemotherapy alone** n= 157
Blood and Lymphatic System Disorders		
Anaemia	14%	18%
Leucopenia	18%	24%
Neutropenia	9%	20%
Febrile Neutropenia	4%	8%
Thrombocytopenia	5%	8%
Metabolism and Nutrition Disorders		
Anorexia	2%	4%
Nervous System Disorders		
Paraesthesia	2%	4%
Eye Disorders		
Conjunctivitis	1%	3%

Adverse Events	**Chemotherapy and CARDIOXANE** n = 375	**Chemotherapy alone** n= 157
Respiratory, Thoracic and Mediastinal disorders		
Dyspnoea	2%	3%
Gastrointestinal Disorders		
Nausea	50%	54%
Stomatitis	16%	34%
Vomiting	51%	38%
Constipation	4%	10%
Diarrhoea	9%	17%
Abdominal pain	2%	4%
Abdominal pain, upper	1%	2%
Dyspepsia	1%	3%
Skin and Subcutaneous Tissue Disorders		
Alopecia	72%	75%
Nail Disorder	2%	3%
General Disorders and Administration Site Conditions		
Asthenia	13%	27%
Mucosal inflammation	3%	14%
Pyrexia	9%	13%
Fatigue	4%	9%
Malaise	8%	1%
Investigative tests		
Ejection fraction decreased	3%	10%

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 3750mg/m^2 when short infusion are given in divided doses over 3 days to 7420mg/m^2 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, an 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^{3+}-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.

From the data available, it is unclear if dexrazoxane alters anti-tumour efficacy of anthracyclines. Based on the current data there is no clear proof that anti-tumour efficacy is affected negatively, but no decrease in overall survival has been noted on limited follow-up to date.

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.

Paediatric patients: There is limited data on safety and efficacy in children. A randomized trial in children with high risk acute lymphocytic leukaemia has demonstrated cardioprotective efficacy based on cardiac troponin T levels as a surrogate endpoint for cardiac damage (see also section 4.2 and 4.4).

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^2 is around 80 μg/ml with area under the plasma

concentration-time curve (AUC) of 130 ± 15mg.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 ± 3.9L, 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.

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

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 gastrointestinal 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 Instructions for use and handling

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 contacts 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 100 ml	50 ml 125 ml	200 ml 500 ml	2.2 3.3
0.16M Sodium Lactate*	25 ml 100 ml	50 ml 125 ml	200 ml 500 ml	2.9 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 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 solution should be discarded in accordance with local requirements. Adequate care and precaution should be taken in the disposal of items used to reconstitute and dilute Cardioxane.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

This is a non-referenced document.