SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CARDIOXANE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of power 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

Prevention of cardiotoxicity in adult women with advanced and/or metastatic breast cancer at high risk of heart failure who have received a prior cumulative dose of 300 mg/m^2 of doxorubicin or a prior cumulative dose of 540 mg/m^2 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^2 when the commonly used dosage schedule for doxorubicin of 50 mg/m^2 is employed or 600 mg/m^2 when the commonly used dosage schedule for epirubicin of 60 mg/m^2 is employed.

Paediatric population
Cardioxane is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Cardioxane in children aged 0 to 18 years have not been established.

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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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/m^2, 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).

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.

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/m^2) or epirubicin (60 to 100 mg/m^2) 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/m^2).

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.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); not known (cannot be estimated from the available data).

Table 1- adverse reactions

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	Embolism
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/m^2 when short infusions are given in divided doses over 3 days to 7420 mg/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, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 Fe^{3+}-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.

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 ± 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

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.

Modeling suggested that equivalent exposure ($AUC_{0\text{-}inf}$) 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

Hydrochloric acid 0.1N

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:
The expiry date of the product is indicated on the packaging materials

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.

After reconstitution and dilution:

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.

6.5 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 vial.

6.6 Special precautions for disposal and other 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 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 100 ml	50 ml 125 ml	200 ml 500 ml	2.2 3.3
0.16 M 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 0.16 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.

7. MANUFACTURER:

Cenexi - Laboratoires Thissen S.A., Braine-l'Alleud, Belgium

8. License Holder:

Megapharm Ltd. P.O. Box 519 Hod Hasharon 4510501

9. Marketing Authorisation Number

109-84-29292

Revised in July 2021 according to MOHs guidelines.

CARD SPC 072021 P.1