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 6.1.

3. **PHARMACEUTICAL FORM**

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

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

The prevention of cardiotoxicity in patients with cancer receiving anthracycline-containing chemotherapy. 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 short intravenous infusion over 15 minutes, approximately 30 minutes prior to anthracycline administration, leaving a 15 minutes break between treatments.

A dose level 20 times the doxorubicin dose level and 10 times the epirubicin dose level should be used. Thus it is recommended that Cardioxane is given at a dose of 1000 mg/m² when the commonly used dosage schedule for doxorubicin of 50 mg/m² or epirubicin 100 mg/m² is employed. The dose of Cardioxane should be adjusted accordingly if that of the anthracycline is reduced for any reason, such as hepatic impairment. No information is available concerning the use of Cardioxane with anthracyclines given by prolonged continuous infusion.

To ensure that the full cardioprotective potential of Cardioxane is realised, it is essential that Cardioxane treatment is initiated with the first dose of anthracycline and it should be repeated each time the anthracycline is administered.

There are no special dosage recommendations for the elderly.

**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.

**Safety and efficacy of Cardioxane in children has not been established.**

**Paediatric patients:** the experience in children is limited (see sections 4.4, 4.8, 5.1 and 5.2).
4.3 Contraindications

- Hypersensitivity to Cardioxane/dexrazoxane.
- Use during pregnancy or in women at risk of pregnancy/ Lactation.

4.4 Special warnings and special precautions for use

This product should only be administered in specialist oncology/haematology units having adequate facilities for appropriate clinical and laboratory monitoring, with particular reference to ECG, haematology and liver function.

Cardioxane should only be administered to patients undergoing cytotoxic therapy with anthracycline containing chemotherapy regimens.

Haematological monitoring should be undertaken regularly, particularly during the first two cycles of therapy. Leukopenia and thrombocytopenia reverse quickly on cessation of therapy.

As there have been reports of liver dysfunction after doses of dexrazoxane exceeding 4.5 times the dose recommended for use as cardioprotector, it is recommended that routine liver function tests are performed in patients with known liver function disorders. Since renal dysfunction may decrease the rate of elimination of dexrazoxane, patients with initial impaired renal function should be monitored for signs of haematological toxicity.

Dexrazoxane has been shown to possess mutagenic activity. The carcinogenic potential of dexrazoxane has not been investigated. Secondary malignancies have not been reported following therapy with dexrazoxane. However, razoxane, the racemic mixture of dexrazoxane, has been reported to be associated with the development of secondary malignancies after administration for a prolonged period of time.

Skin reactions have been reported following contact with Cardioxane. 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 1000 mg/m², 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.

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

In clinical trials, second malignancies 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).

Since dexrazoxane is a cytotoxic agent, with topoisomerase II inhibition activity, combination of dexrazoxane with chemotherapy may lead to an increased risk of second malignancy.

4.5 Interaction with other medicinal products and other forms of interaction

Cardioxane may potentiate the 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 is no conclusive information as to whether Cardioxane may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that Cardioxane is foetotoxic and should, therefore, not be administered to pregnant women or to mothers who are breast feeding.

Cardioxane should not be administered to fertile persons not practicing effective contraception. 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

It is unlikely that Cardioxane will affect the ability to drive or use machines, as it has not been found to have any effects on the central nervous system. 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, has not been found to increase the incidence or severity of clinical signs of toxicity of a standard chemotherapy regimen consisting of 5-fluorouracil, doxorubicin and cyclophosphamide, anthracycline based regimens, with the exception of a small but definite accentuation of leukopenia (including neutropenia and febrile neutropenia) and thrombocytopenia 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 anaemia, or even bone marrow aplasia. Also injection site pain and local irritation have been reported. Hypersensitivity reactions rarely occur. The relative contribution of Cardioxane and chemotherapeutic agents is unclear.

Deep Venous Thrombosis (DVT) with possibility of fatal pulmonary embolism has been reported. The exact contribution of Cardioxane to this event is difficult to assess, as there are confounding factors such as the impaired status of the veins in these cancer patients, impaired mobility, and other medication given.

At much higher doses (4500 mg/m$^2$, Maximum Tolerated Dose), transient mild to moderate leucopenia, transient mild thrombocytopenia, nausea, vomiting, alopecia and transient elevations in liver function values have been observed. Other toxicities reported at dexrazoxane doses at the MTD level 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.

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, hypersensitivity (see also section 4.4).
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) 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/m$^2$ (median: 1000 mg/m$^2$) in combination with doxorubicin, and a mean dose of 941 mg/m$^2$ (median: 997 mg/m$^2$) in combination with epirubicin.
- Chemotherapy treatment received by patients treated for breast cancer: 45% combination therapy with doxorubicin 50 mg/m$^2$ (mainly with 5-fluorouracil and cyclophosphamide); 17% with epirubicin alone; 14% combination therapy with epirubicin 60 or 90 mg/m$^2$ (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

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Chemotherapy and Cardioxane</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>n = 375</td>
<td>n = 157</td>
</tr>
<tr>
<td>Anaemia</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9%</td>
<td>20%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasthesia</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16%</td>
<td>34%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51%</td>
<td>38%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>13%</td>
<td>27%</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Malaise</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Investigative tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>3%</td>
<td>10%</td>
</tr>
</tbody>
</table>
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, 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.

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.

4.9 Overdose

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

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: V 03 AF 02

Dexrazoxane, an analogue of EDTA (ethylenediaminetetraacetic acid), is hydrolyzed 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 the uptake and subsequent hydrolysis of dexrazoxane in the myocardium protects against doxorubicin-induced cardiotoxicity by the scavenging of metal ions from their potentially damaging complexes with doxorubicin, and by preventing the Fe³⁺-doxorubicin complex from redox cycling and forming reactive radicals.

As the cardiotoxicity and anti-tumor activities of doxorubicin are mediated through different mechanisms, dexrazoxane does not affect the anti-tumor efficacy of doxorubicin, nor does it protect against non-cardiac toxicities induced by doxorubicin. 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.
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 randomised 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 sections 4.2, 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. Mean $t_{1/2}$ values are approximately 15 minutes, mean $t_{1/2}$ values approximately 140 minutes. 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 ± 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 1.1 l/kg ± 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 ± 1.6 l/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. Tissue distribution is rapid, with the highest levels of unchanged parent drug and hydrolysed product appearing in liver and kidneys. Dexrazoxane does not penetrate into the cerebrospinal fluid to a clinically significant extent.

Total urinary recovery 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. Drug clearance may be reduced in patients with low creatinine clearance. Significant serum protein binding has not been observed, less than 2% of dexrazoxane is protein bound. 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 normalised for body surface area are not significantly different from those of adults.
5.3 Preclinical safety data

A single i.v. dose of 600 mg/kg in rats and mice did not cause mortality or significant toxicity. Preclinical studies indicate that with repeated dose dexrazoxane administration, the primary target organs of dexrazoxane 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 alteration toxicity produced; a single high dose is better tolerated than the same dose divided over daily administrations.

Dexrazoxane has been shown to possess mutagenic activity in the mouse micronucleus assay in vivo. It cannot be excluded that dexrazoxane may have carcinogenic properties. 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

Hydrochloric Acid Not applicable

6.2 Incompatibilities

Incompatibilities with other drugs, medicinal products or materials are not known. Cardioxane should however not be mixed with other drugs during infusion, other than the diluents mentioned in section 6.6.

6.3 Shelf life

The Cardioxane expiry date is 3 years from the date of manufacture. Once reconstituted store for 4 hours at 2-8°C.
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

Do not store the lyophilized product above 25°C.
Before opening: Do not store above 25°C. In order to protect from light store in the original package.
From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours at 2-8°C.

After dilution of the reconstituted product with an appropriate infusion fluid, Cardioxane should be used immediately.

6.5 Nature and contents of container

Cardioxane is packaged in single use 36 ml vials of brown, light resistant, type I (Ph.Eur.) glass, closed with a chlorobutyl rubber stopper and an aluminium flip-off cap. Each vial contains 500 mg of the active ingredient in its hydrochloride form.

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 (see section 4.4). Caution in the handling and preparation of the powder and solution must be exercised and the use of gloves is recommended. 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 25.0 ml Sterile Water for Injections. The vial contents will dissolve within a few minutes with gentle shaking. The resultant solution has a pH of approximately 1.6. 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 not be infused without further dilution with Ringer Lactate Solution or 0.16 M Sodium Lactate Solution USP. 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 following table summarizes the final volume and the approximate pH of reconstituted and diluted product for after dilution of one vial and four vials of Cardioxane, or after dilution of 4 vials of Cardioxane with the recommended infusion fluids (t. The minimum and maximum volumes of infusion fluids to be used per vial are presented shown below.

<table>
<thead>
<tr>
<th>Infusion fluid used for dilution</th>
<th>Volume of infusion fluid used to dilute 1 vial containing</th>
<th>Final volume obtained for 1 vial</th>
<th>Final volume obtained for 4 vials</th>
<th>pH (approximate)</th>
</tr>
</thead>
</table>

Page 9 of 11
<table>
<thead>
<tr>
<th>25ml of reconstituted Cardioxane</th>
<th>25 ml</th>
<th>50 ml</th>
<th>200 ml</th>
<th>2,2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringer lactate</td>
<td>25 ml</td>
<td>50 ml</td>
<td>200 ml</td>
<td>2,2</td>
</tr>
<tr>
<td></td>
<td>100 ml</td>
<td>125 ml</td>
<td>500 ml</td>
<td>3,3</td>
</tr>
<tr>
<td>0.16M Sodium Lactate*</td>
<td>25 ml</td>
<td>50 ml</td>
<td>200 ml</td>
<td>2,9</td>
</tr>
<tr>
<td></td>
<td>100 ml</td>
<td>125 ml</td>
<td>500 ml</td>
<td>4,2</td>
</tr>
</tbody>
</table>

* 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 per vial of additional infusion fluid per 25ml reconstituted Cardioxane) is usually recommended in order to increase the pH of the solution. Smaller dilution volumes (with a minimum of 25 ml per vial of Cardioxane 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. Discard any remaining contents. Reconstituted and subsequently diluted product should be used immediately or within 4 hours if stored between 2°C and 8°C.

Note: Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever 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

8. MARKETING AUTHORISATION NUMBER

PA 13/121/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 1993 / 22 October 2003

10. DATE OF REVISION OF THE TEXT

March-July 2010