14-006-001CA-21

CARDIOXANE®

CHIRON

NAME

Cardioxane®

COMPOSITION

Cardioxane contains 500 mg lyophilized dexrazoxane, as its hydrochloride salt. The chemical name of dexrazoxane is (S)-(+)-1,2-bis(3,5-dioxopiperazinyl)propane, its commonly used code name ICRF-187. Cardioxane contains no excipients or preservatives.

PHARMACEUTICAL FORM

Sterile, white to off-white, lyophilized powder for infusion.

PHARMACOLOGICAL PROPERTIES

Mechanism of action

There is considerable evidence to suggest that the dose-dependent cardiotoxicity that occurs during doxorubicin administration may be due to doxorubicin-induced iron-dependent free radical oxidative stress on the relatively unprotected cardiac muscle.

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 Fe^{3+}-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.

Pharmacokinetics

After intravenous administration serum kinetics of dexrazoxane follow an open two-compartment model. Mean $t_{1/2}\ \alpha$ (values are approximately 15 minutes, mean $t_{1/2}\ \beta$ values approximately 140 minutes. The apparent volume of distribution is 1.1 l/kg. 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 of unchanged dexrazoxane is in the order of 40%. 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.

CLINICAL PARTICULARS

Indication

Prevention of cardiotoxicity in patients undergoing cytotoxic therapy with doxorubicin containing chemotherapy regimens.

Contra-indications

Hypersensitivity to Cardioxane.

Undesirable effects

At the doses recommended for cardioprotection, Cardioxane 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, with the exception of a small but definite accentuation of leukopenia and thrombocytopenia. 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.

Special precautions for use

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.

Like other cytostatic drugs Cardioxane should be administered under the direction of those experienced in cytotoxic therapy.

Skin reactions have been reported following contact with Cardioxane. 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, immediately rinse the affected area thoroughly with water.

Use during 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 may harm the foetus 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.

Interactions

Cardioxane may potentiate the toxicity induced by chemotherapy or radiation, requiring careful monitoring of haematological parameters during the first two treatment cycles.
Cardioxane should not be mixed with any other drug during infusion.

Posology and method of administration

Cardioxane is administered by short intravenous infusion over 15 minutes, approximately 30 minutes prior to doxorubicin administration, at a dose level 20 times the doxorubicin dose level. 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 every 21 days is employed, however the total dose of Cardioxane should never exceed the 1000 mg/m^2

Cardioxane treatment should be initiated simultaneously with the first dose of doxorubicin and should be repeated each time doxorubicin is administered.

There are no special dosage recommendations for the elderly.
Safety and efficacy of Cardioxane in children have not been established.

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. To avoid the risk of thrombophlebitis at the injection site, Cardioxane should not be infused without further dilution.

The contents of the appropriate number of vials should be mixed aseptically and diluted to a volume of 200-250 ml with Ringer Lactate solution, 0.16 M Sodium Lactate solution USP or phosphate buffer.
Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Overdosage

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

Special warnings

Cardioxane should only be administered to patients undergoing cytotoxic therapy with doxorubicin-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. To ensure that the full cardioprotective potential of Cardioxane is realised, it is essential that Cardioxane treatment is started at the time of the first dose of doxorubicin.

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.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Incompatibilities with other drugs or materials are not known. Cardioxane should however not be mixed with other drugs during infusion.

Shelf-life

Cardioxane should not be stored beyond the expiration date marked on the vial and the carton.
Since Cardioxane contains no antimicrobial preservatives it is recommended to start the administration of the solution promptly after reconstitution/dilution.

Special precautions for storage

Store the lyophilized product at or below 25 °C. Protect from light and moisture. The diluted product should be stored protected from light at 2-8 °C and used within 4 hours. Any unused solution should be discarded.

Nature and contents of the container

Cardioxane is packaged in single use 36 ml vials of brown, light-resistant, type I 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.

Manufacturer

Chiron B.V., Paasheuvelweg 30, 1105 BJ Amsterdam, The Netherlands.

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CHIRON