SCIENTIFIC DISCUSSION

1 Introduction

Extravasation of cytotoxic agents is the unintentional instillation or leakage of these agents into the perivascular or subcutaneous spaces during their administration (Cox et al, 1988).

Cytotoxic drugs are often infused intravenously through peripheral lines. Although central venous access devices, such as implantable venous ports and central venous catheters (CVC), have become useful options, extravasation injury may also occur and poses special problems in the treatment due to the embedded site of the catheter.

Extravasation of cytotoxic agents occurs rarely but is a feared complication, especially from drugs such as the anthracyclines, mitomycin C, vincristine, and vinorelbine. Doxorubicin and daunorubicin account for most clinical extravasation reports. If a treatment is not established as soon as realization of the accident, severe complications may occur, leading to: progressive necrosis of skin and subcutaneous tissue, nerve, vascular, tendon and articular damage, surgical resection often necessitating skin grafting, pain and functional defects, hospitalisation, interruption of cancer chemotherapy.

The clinical picture of the natural course of anthracycline extravasation consists of different phases. The initial phase, characterised by immediate pain, oedema/swelling, erythema, blistering is followed by a marked brownish induration lasting for days to months. In some patients, after 1-4 weeks ulceration of the induration occurs, initially perhaps a small ulcer, but it will constantly enlarge for 1-3 months without tendency for spontaneous healing and will assume invasive character extending to deep structures and underlying tendons and joints without respecting fascia. Infection is often superimposed. The ulcer is largely avascular and without significant inflammatory response. The risk of ulceration is related to the concentration and amount of extravasated anthracycline. Long-term pain, contractures, dystrophy, loss of function of affected limb may follow.

Symptoms from a central venous catheter may be somewhat different and with delayed onset. Chest wall infiltration may present as shoulder pain and mediastinal leakage as substernal pain.

At the time of submission of the marketing authorisation application for Savene for the treatment of anthracycline extravasation no medicinal product had been authorized in this indication.

Non-surgical methods currently in use for the treatment of suspected anthracycline extravasation are immediate discontinuation of the infusion and an attempt to aspirate the site for residual drug before removing the catheter. In most institutions, local cooling (to produce vasoconstriction preventing spread, and provide pain reduction), and administration of corticosteroids and dimethylsulfoxide (DMSO, a solvent that enhances skin permeability and thus facilitates absorption and recuperates anthracycline-generated free radicals.

Existing non-surgical methods have not proven up till now to be always effective.

Dexrazoxane is a bisdioxopiperazine that readily enters cells and is subsequently hydrolysed to form a chelating agent analogous to EDTA, the two-ring opened metabolite, ICRF-198 / ADR-925. This chelating property is proposed to be its mechanism of action in the prevention of anthracycline-induced iron-dependent free radical oxidative stress on the cardiac muscle. Dexrazoxane is also a catalytic inhibitor of DNA topoisomerase II. Dexrazoxane has been in clinical use since 1981.
Initially, it was considered as an antineoplastic agent but the antineoplastic potential was insufficient for further development. It was then found to protect against the cardiotoxicity of anthracyclines. In Europe, since 1992, there is a marketed formulations of dexrazoxane licensed for the prevention of cardiomyopathy associated with doxorubicin administration.

Researches conducted since 1991 indicate that dexrazoxane is also a specific catalytic inhibitor of DNA topoisomerase II in that it is able to lock the enzyme's N-terminal clamp while simultaneously inhibiting its ATPase activity. The new results indicate that dexrazoxane blocks the induction of DNA strand-breaks by anthracyclines and that may be involved in the amelioration of anthracycline toxicity. (Tanabe et al., 1991; Sehested et al., 1993; Langer et al., 2000).

2 Quality aspects

Introduction

Savene is presented as powder and diluent for solution for infusion.
Savene powder contains 20 mg/ml corresponding to 500 mg of dexrazoxane (as hydrochloride) supplied in an amber coloured, light-resistant, Type I glass vial closed with rubber stoppers and either an aluminium cap with a polypropylene disc on top.

Savene diluent is presented as an isotonic solution for infusion, packaged in a 500 ml flexible plastic container.

It is packaged in a box containing 10 vials and 3 bags of 500 ml diluent for solution for infusion.
It is intended to first reconstitute the powder with Water for Injections and then add it to the diluent prior to administration.

Active Substance

The active substance is a white to off-white crystalline powder, soluble in 0.1N HCl and sparingly soluble in water. Dexrazoxane is the INN name of the active substance 2,6-Piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis-, (S)-. The molecule shows an asymmetric centre and the S (+) form is used in Savene. No polymorphic forms have been identified during the development.

- Manufacture

The active substance is synthesised by multiple steps and purified to high optical purity material.

Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

- Specification

The active substance specification includes tests for appearance, solubility, identity (IR, HPLC), melting point (PhEur), purity (UV-VIS) assay (HPLC)/ assay basic function, purity and related substances HPLC, chiral purity (chiral HPLC), specific rotation, content of R(-) enantiomer, residual solvents (GC), residue on ignition, and water content. Furthermore, particle size and bulk density are reported for information purpose only. Results from three batches confirm the suitability of the active substance specification approved.

- Stability

Stability studies in both long-term and intermediate conditions (30°C/60%RH) showed that dexrazoxane was stable at long-term conditions and remained within the specification during the whole accelerated study. The results of the long-term and accelerated studies comply with the proposed specifications and justify the proposed retest period.

Medicinal Product

- Pharmaceutical Development

Powder

Pharmaceutical development of Savene focused on obtaining a formulation containing > 250 mg of Dexrazoxane per vial, which would easily dissolve in water and be stable after reconstitution under the circumstances specified in the SPC.

The desired efficacy of dexrazoxane in clinical practice is achieved when administered in a three-day schedule with 1000 mg/m^2 administered for the first 2 days and 500 mg/m^2 administered the third day. Hence, the standard dose (based upon a 70 kg person with a 1.8 m^2 body surface area) will be 1800 mg/patient per treatment day 1 and 2 and 900mg/patient day 3. Consequently, the formulation of 500 mg dexrazoxane/vial was considered optimal, since lower dexrazoxane content would require too many vials per treatment while a higher content would complicate the manufacturing process.
Dexrazoxane is the S-enantiomer of the racemic mixture of Razoxane. Due to its low solubility, Razoxane cannot be formulated for parenteral use and is erratically absorbed when administered orally. Dexrazoxane is more soluble in water than Razoxane, which allows parenteral administration. Dexrazoxane is poorly soluble in its base form, and in order to obtain a more soluble form, the drug substance is converted into its hydrochloride salt. Development studies have shown that it is soluble in 0.1 N hydrochloric acid with an acceptable dissolution rate. Due to the limited stability of dexrazoxane in aqueous solutions a liquid or solution dosage form of Savene was not feasible, therefore a solid dosage form was developed.

Various factors were optimised during pilot and commercial scale formulation and process.

Diluent

Savene diluent is an isotonic solution consisting of Water for Injections, Sodium hydroxide and pharmacopoeial grade salts. These are: Sodium chloride, Potassium chloride, Magnesium chloride hexahydrate, Sodium acetate trihydrate and Sodium gluconate.

The manufacturing of the bulk solution is a standard process for an aqueous solution. The solution is then filled into the plastic container and terminally sterilised using moist heat with a steam sterilisation cycle.

The infusion bag and port system are composed of materials complying with the Ph.Eur, or the French Pharmacopoeia.

The compatibility of Savene powder with several potential infusion liquids has been screened. However, Savene diluent is the diluent of choice for stability and patient tolerance reasons and therefore, it is mentioned in the SPC and included in the presentation of the Medicinal Product.

- Adventitious Agents

Dexrazoxane powder does not contain any materials of animal origin.

- Manufacture of the Product

Manufacturing process involves the following steps: preparation of the bulk solution, sterilisation by filtration, aseptic filling, lyophilisation and washing of the outside of the vials and visual inspection.
The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process, and is satisfactory. All results from the in-process controls were within the specifications.
The batch analysis data show that the product can be manufactured reproducibly according to the agreed finished product specification.

- Product Specification

The specification for Savene powder includes tests for appearance/colour, uniformity of mass (Ph. Eur.), identification of dexrazoxane (IR, HPLC), identification of Chloride (Ph. Eur.), dexrazoxane assay (HPLC), uniformity of content (Ph. Eur.), and purity (HPLC).
The current specifications for Savene powder were established over statistical evaluation of data from 89 batches.

The specification for Savene diluent includes tests for appearance, identification, assay, pH, sterility bacterial endotoxins, sub-visible particles, extractable volume and leachables. All tests are performed using suitable validated methods.

The specification for Reconstituted Product includes tests for clarity, colour, particulate, rate of dissolution, pH, endotoxins and sterility according to Ph. Eur.
The tests and limits of the specifications Savene powder, diluent and the Reconstituted Product are appropriate to control the quality of the finished product for the intended purpose.

- Stability of the Product

The on-going stability studies on Savene powder (long-term and accelerated) are being conducted on batches containing stoppers supplied by the two different suppliers according to the current ICH guidelines.

Other batches were stored (in the commercial packaging) for the full shelf life at 25°C. Some of these batches have been stored at 4°C and 60°C. The results of these studies are provided as supportive data.

Drug Product vials were analysed for appearance, content of dexrazoxane, impurities A, B, C, moisture and sterility (initial and at the end of the study), and the solution after reconstitution was evaluated for colour, pH and completeness/clarity of dissolution.

The test methods used for the stability testing are equivalent to the ones used for Quality Control testing for the release of commercial product.

Concerning the diluent, stability data for 50, 100 and 1000 ml bags have been provided. The samples are stored in the proposed commercial packaging. In addition to the above conditions containers have been subjected to resistance to thermal stress at design verification and final validation stages. No significant adverse effects have been observed.

The parameters and test methods used for routine release testing are applied to the stability trials. Additionally, visual inspection (black and white background), colour test (Ph. Eur.), leachables determination and extractable volume determination have been performed.

Weight Loss (WL) / Volume Loss (VL) has been performed using other products stored in the same container.

Concerning the product as a whole, based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

- In-Use Stability study on reconstituted and diluted Savene.

The stability of the reconstituted product in water for injection has been investigated.

Savene is stable for 4 hours after reconstitution and subsequent dilution in Savene diluent when stored under the conditions specified in the SPC. (see SPC section 6.3).

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

3 Non-clinical aspects

Introduction
Dexrazoxane is the S(+)-enantiomer of the racemate razoxane and acts as a detoxifying agent, most likely by inhibition of topoisomerase II, for antineoplastic agents.

Pharmacology
None of the primary and secondary pharmacodynamics studies were made according to GLP.

- Primary pharmacodynamics

A model, where subcutaneous (s.c.) injection of anthracyclines such as doxorubicin and daunorubicin to the back of female mice produced skin necrosis for four to six weeks, has been used in all studies carried out by the applicant to evaluate the protective effect of dexrazoxane against extravasation following anthracycline administration.

Following daunorubicin, doxorubicin or idarubicin-induced extravasation of 3 mg/kg in the mouse model, a single intraperitoneal (i.p.) dose of dexrazoxane (62.5-375 mg/kg) significantly reduced the occurrence of skin wounds. In mice given a 3 mg/kg doxorubicin injection s.c., doses with 62.5 mg/kg dexrazoxane i.p. repeated every three hours three times resulted in two experiments in an absence of skin wounds in the mice compared with a 61 and 100% skin wound occurrence in the control mice. In mice with doxorubicin-induced skin wounds, a single dose of 250 mg/kg dexrazoxane i.p. completely prevented skin wound occurrence after experimental extravasation with 2 or 3 mg/kg doxorubicin or decreased the AUC of wounds significantly. In a timing study with 3 mg/kg doxorubicin extravasations, the frequency of wounds increased when treating with 250 mg/kg dexrazoxane 6 hours after experimental doxorubicin extravasation: At treatment 6 h after doxorubicin s.c., wound frequency was 44% compared to 19 and 11% at treatment at t=0 or 3 h after extravasation, respectively.

Using single high doses of 250 mg/kg dexrazoxane on day 0, 1 and 2 had good effect on skin wound size and duration, as the mean AUC of the wounds was 170.3 mm² days compared with 1546 mm² days in saline-treated mice given 3 mg/kg daunorubicin s.c. The dose of 62.5 mg/kg dexrazoxane and treatment schedule of q3h x 3 on the same day as the experimental extravasation was sufficient to treat a 6 mg/kg doxorubicin extravasation in the mice, as 8% of the mice developed a skin wound after this treatment compared with 12% of mice developing skin necrosis when the treatment was extended to three consecutive days.

Comparison of the i.p. and i.v. treatment route of 250 mg/kg dexrazoxane resulted in similar skin wound frequencies: Of mice with experimental daunorubicin extravasation, 67% given dexrazoxane i.v. had skin wounds *vs.* 87% of mice given dexrazoxane i.p. (p=0.58). After dexrazoxane treatment, 22% in mice treated with dexrazoxane using the i.v. route had wounds and no mice after i.p. dexrazoxane (p=0.47). The skin wound size and duration was smaller in mice given i.p. dexrazoxane after s.c. daunorubicin compared with mice treated i.v. (p=0.07).

The effect of dexrazoxane on idarubicin or epirubicin-induced extravastion was not statistically significant, showing no difference in the wound frequency or AUC (p=0.59).

Placing an ice pack for 0.5 hour to the daunorubicin-affected skin area did not change the effect of 62.5 mg/kg dexrazoxane given q3h three times after the extravasation, as none of the treated mice developed skin wounds following the treatment, but all mice treated with the ice pack alone for 0.5 h had skin wounds. Intra-lesional injection of 125 mg/kg hydrocortisone alone and combining this treatment with systemic dexrazoxane 62.5 mg/kg q3h three times did not change the protective effect of dexrazoxane against skin wounds. Topical treatment with pure dimethylsulfoxide (DMSO) three times daily for four days following the accidental extravasation did not decrease skin wound size and duration compared to mice given saline topically in the same schedule as the DMSO (p=0.41). Topical DMSO treatment, added to the three 62.5 mg/kg doses of dexrazoxane, increased the frequency of skin wounds from no skin wounds in the dexrazoxane-treated mice to 7/9 mice having wounds.

The mechanism of action of dexrazoxane was investigated in comparison studies with various other adjuvant treatment. Neither EDTA, given as single i.p. doses of 62.5- 250 mg/kg, nor ADR-925 after injection of 3 mg/kg daunorubicin s.c. did prevent skin necrosis or decrease the AUCs of the skin wounds. The free radical binding cytoprotectant amifostine (100 -200 mg/kg) had no effect on AUC or occurrence of skin wounds. Single doses of 500 and 1000 mg/kg N-acetylcysteine or 62.5 -200 mg/kg alpha-tocopherol were also given to groups of mice after a daunorubicin injection s.c. without any effect on occurrence or size/duration of skin wounds. The catalytic inhibitors of topoisomerase 2, aclarubicin (10 or 20 mg/kg i.p. to mice after s.c. daunorubicin injection), and merbarone (50- 100 mg/kg i.p. after s.c. daunorubicin), had no effect on skin wound frequency or size/duration.

- Secondary pharmacodynamics

A review of the literature showed that pre-treatment with dexrazoxane reduced anthracycline-induced cardiotoxicity in mice, rats, rabbits, dogs and mini-pigs. Male rabbits, given 12.5-25mg/kg dexrazoxane i.p. 30 min. before 3.2mg/kg i.v. daunorubicin once every three weeks five times, showed significant lower cardiomyopathy scores [1, 2]. In beagle dogs, given 1 mg/kg doxorubicin as a bolus injection i.v. once weekly 15 times and 12.5 mg/kg dexrazoxane i.p. 30 minutes before the doxorubicin injection, a significant reduces cardiomyopathy score was observed compared to the control group without dexrazoxane [2]. In mice, given 50 mg/kg dexrazoxane i.p. 30 minutes before 4 mg/kg doxorubicin i.p. two times weekly on weeks 1, 2, 5, 6 and 7, 53% of mice receiving doxorubicin had myocardial changes vs. 18% in the dexrazoxane-doxorubicin treated group [3]. Chronic doxorubicin administration in rats and evaluation at 5 weeks using electron microscopic evaluation [4], or at various time points up to 28th week after the last treatment was given using light microscopic evaluation [5], showed that different doses of dexrazoxane protected against microscopic signs of doxorubicin-induced cardiomyopathy.

Studies dating back to the 1960's showed that razoxane has antineoplastic activity against L1210 leukaemia, sarcoma 180 and Ca 755 tumours. In one study with leukaemic mice, given a split dosage regimen of dexrazoxane (16 mg/kg i.p., every 3 h on days 1, 5 and 9) an increased mean survival time was observed [6].

- Safety pharmacology programme

The safety pharmacology studies were conducted according to GLP regulations, but due to prior performance not in accordance to ICH S7A.

Administration of dexrazoxane 50, 100 and 200 mg/kg did not have an effect on spontaneous locomotor activity, motor coordination using rotarod and intestinal motility in mice. Dexrazoxane (200mg/kg) resulted in a significant increase in hexobarbital induced sleeping time in mice. There was no significant effect with the lower doses of dexrazoxane. Administration of dexrazoxane 100 mg/kg caused a significant decrease in the urine output in rats at 4 and 5 hours post dose. No significant effects were noted with the higher and lower doses. There was no significant effect on urinary electrolyte excretion with any of the doses. There were no cardiovascular and respiratory effects recorded following administration of 25, 50, 100 mg/kg dexrazoxane in anaesthetized dog.

- Pharmacodynamic drug interactions

No specific studies for this indication were conducted. *In vitro* dexrazoxane and docorubicin interacted synergistically to enhance sarcoma S180 cell kill [7].

Pharmacokinetics
Pharmacokinetics of dexrazoxane was investigated *in vivo* in two studies with rats and dogs (by Inveresk International) and supplemented by a review of published literature.

- Absorption-Bioavailability

In studies, in which male mice received a 50 mg/kg dose of [14C]dexrazoxane i.v. (Narang *et al*., 1988), kinetic analysis of plasma [14C] levels measured over time demonstrated the adequacy of a three compartment model, with associated half-lives (t1/2) of 3.5 min, 30 min and 4.8 h, respectively. In a separate study (McPherson *et al.*, 1984), mice were treated i.v. (100 mg/kg) with dexrazoxane, and plasma t1/2α- and t1/2β values of 3 min and 23 min, respectively, were reported.

After a single bolus intravenous administration of [14C]dexrazoxane (20 mg/kg) in the rat, the plasma total radioactivity level fell in males (female data in parentheses) from a maximum of 45.7 (45.4) µg/ml at 2 min post-dose, to mean values of 5.1 (7.4) – and 0.1 (0.2) µg/ml at 1- and 8 h post-dose, respectively. The AUC (0 – 8 h), was approx. 20 µg /ml for males and 25µg /ml for females. When rats were pre-treated with doxorubicin (1 mg/kg; i.v.), prior to administration of [14C]dexrazoxane, all observed plasma data sets were similar to those above, except that the male peak radioactivity level was initially higher (90.1 µg/ml).

In rats, plasma razoxane levels followed a biphasic pattern of decay (mean initial and terminal phase half-lives were 11.7- and 40.3 min, respectively) following i.v. administration (21.75 mg/kg), and following oral administration, the peak plasma level (3.7 µg/ml; 30 min) declined mono-exponentially with a half-life of 78.4 min. The ratio of the AUC curves for oral versus i.v. administration was 0.53, showing a limited bioavailability of oral razoxane.

Razoxane (100 mg/kg) was absorbed quickly from the peritoneal cavity in rats, reaching a peak plasma concentration (12.0 µg/ml; 15 - 30 min), which decayed mono-exponentially following first-order kinetics (t1/2 approx. 1.6 h).

In dogs, receiving a single i.v. 20 mg/kg dose of ^{14}C-dexrazoxane, the plasma total radioactivity level fell from a maximum of 63.5 µg/ml at 2 minutes post-dose, to a mean value of 15.7 -, 0.4 - and 0.1 µg/ml at 1-, 8- and 24 hours post-dose, respectively. The mean $AUC_{0-24\ h}$ was approx. 60 µg/ml. Plasma radioactivity levels were at or near the level of detection by 48 hours post-dose. In the dog, a two-compartment open model adequately described the dexrazoxane plasma concentration versus time data (single iv administration; 10 –100 mg/kg) and a terminal plasma half-life of 1.1 - 1.3 h was reported.

- Distribution

After a single bolus i.v. administration of [14C]dexrazoxane (20 mg/kg) in the rat, the tissue distribution of total radioactivity was similar for both sexes (from 5 min to 96 h post-dose). Levels were highest in the kidney (80 and 100 µg/g, males and females, respectively), liver (50 and 52 µg base equiv./g, males and females, respectively) and bone marrow (54 and 37 µg base equiv./g, males and females, respectively) at 5 min post-dose. In all other organs and tissues the radioactivity was similar to or less than in plasma at each time. Elimination from organs and tissues was at a similar rate as from plasma, indicating that significant accumulation did not occur. Binding of dexrazoxane to plasma proteins was minimal in the rat (5%; 50 mg/kg) and the dog (Baldwin et al, 1988), and the blood cell to plasma partitioning ratio (approx. 0.517; dog) indicated that the drug resided predominantly in the plasma. The steady-state volume of distribution was limited.
The cerebrospinal fluid (CSF)-penetration of ^{14}C-dexrazoxane was investigated in rhesus monkeys [8]. In the animals, receiving i.v.25 mg/kg dexrazoxane spiked with 1.2 mg of ^{14}C-dexrazoxane (37 µCi/mg), the CSF dexrazoxane levels were shown to be limited to 10% of the (bound and unbound) plasma concentration.

- Metabolism

In vitro dexrazoxane was hydrolysed slowly (pH 7.4, 37 °C), in a non-enzymatic (hydroxide-catalysed) fashion to Intermediates B and C (t1/2 = 8 - 9 h), and to ADR-925 (t1/2 = 23 h)[9]. Dihydropyrimidine Amidohydrolase (DHPase) contained within the soluble fraction of liver and kidney tissue homogenates, significantly enhances the hydrolysis of dexrazoxane, to form intermediates B and C, but is unable to effect full hydrolysis, to form ADR-925[10]. DHPase exhibits stereospecificity and acts four fold faster on dexrazoxane than on levrazoxane, and intermediate B is formed faster (≥ 1.5 – fold) than intermediate C. Dihydroorotase (DHOase) catalyses the full ring-opening of intermediates B and C resulting in ADR-925, but shows no activity towards neutral dexrazoxane. DHOase is present in various tissues like the heart, liver and kidney.
In two *in vivo* studies after a single i.v. dose of ^{14}C-dexrazoxane (20 mg base/kg) in rats[11], or dogs, two major radioactive compounds were found in plasma, with retention times similar to ADR-925 and dexrazoxane. In dogs the same two major components were detected in urine. The same two major components plus a third radiolabelled compound (with a retention time of 12 minutes similar to that of the one ring opened product) were also present in rat urine and/or faeces samples. Dexrazoxane accounted for approximately 56% and 51% of the dose collected 0-24 hours post dose in male and female rats, respectively.

- Excretion

Studies in which the animals received a 50 mg/kg i.v. dose of [14C]dexrazoxane, demonstrated that the cumulative urinary- and faecal recovery over 0 - 72 h, was 89 –90 % and 10 %, respectively for mice (Narang *et al*., 1988) and rats (Baldwin et al 1988). In dogs the major route of excretion was via the urine, which accounted for 64 - 91 % of the administered dose. Excretion of radioactivity was rapid with 69-86% and 54 - 87 % of the dose recovered in urine in the first 8 hours in rats and dogs respectively, and approx. 79 % recovered in the first 24 hours. Excretion via the faeces accounted for 2 - 7 % of the dose.

Mean elimination half life over 8 hours, $t_{1/2}$ (0 – 8 h), was 0.5 and 0.7 hours after a single i.v. dose of [14C]dexrazoxane for male and female rats, respectively. Pre-treatment with doxorubicin did not change the plasma kinetics. Higher levels of radioactivity remaining in the heart of rats 96h post-dose than in other tissues showed a slow rate of elimination in this organ. The $t_{1/2}$ (0 – 8 h) value was approximately 0.8 hours for the dog.

In a study [12], in male beagle dogs, the systemic clearance (CL) ranged from 10.3 ± 0.8- to 11.5 ± 2.5 ml/min/kg, and over the dose range evaluated (10 – 100 mg/kg), CL was dose independent. The mean renal Clearance (CLR) contributed approx. 37 % to the systemic clearance. Dexrazoxane was

subject to low organ extraction, and large quantities of unchanged drug were found in liver and kidney extracts, and in plasma and urine.

- Pharmacokinetic Drug Interactions

Published literature on pharmacokinetic drug interaction between dexrazoxane and doxorubicin have produced conflicting results depending on the individual studies.
In one study [4], dexrazoxane significantly enhanced doxorubicin uptake in myocardial tissue in female rats. In another study [13], dexrazoxane inhibited the binding of doxorubicin to red blood cells in a concentration-dependent manner, reduced the binding of doxorubicin to haemoglobin *in vitro,* and exerted a significant reduction in various doxorubicin-associated pharmacokinetic variables in rats *in vivo* [13], (e.g., lowered the volume of distribution and plasma concentration of doxorubicin, reduced AUC and mean residence time). A third study [14] showed that dexrazoxane had no major effect on doxorubicin (or doxorubicinol) pharmacokinetics in plasma or heart tissue of either young or old rats, and a fourth study [15] showed that dexrazoxane had no significant effect on the disposition of doxorubicin in dogs. Other pharmacokinetic studies

No other pharmacokinetic studies have been conducted.

Toxicology

- Single dose toxicity

Single dose toxicity data was provided by two GLP-compliant studies in mice (RCC Notox 018753) and rats (RCC Notox 018742) and by data published in the scientific literature.

After administration of 600 mg/kg dexrazoxane i.v. within 24 hours to Albino CD-1 strain mice, no clinical signs of toxicity were obsereved, but enlarged spleen in 2/10 animals. A single i.v. dose schedule of 1000 mg/kg dexrazoxane given to a group of 20 CDF1 mice did not produce toxicity or lethality. In a study with mice, receiving single doses of 50- 500 mg/kg i.p. dexrazoxane combined with topoisomerase 2 poisons (doxorubicin, daunorubicin, etoposide), the highest dose of dexrazoxane resulted in a leucocyte nadir, as the mean WBC count dropped to to around 2 x 10^9 cells/L compared with a pre-treatment value of ca. 4 x 10^9 cells/l [16]. Examination of the jejunum after single dose of dexrazoxane up to 675 mg/kg i.p. showed no changes in jejeunal crypts of mice [17]. In a study with Albino Wistar rats (5 male and 5 female), receiving a total of 600 mg/kg dexrazoxane i.v. within 24 hours, no mortality occurred, but all males showed severe oedema of the cervical region and/or the legs. Macroscopic examination at necropsy of all animals revealed in 6/10 animals an enlarged spleen. In Wistar rats, 3 hours after dosing with 100mg/kg dexrazoxane i.p., increased liver protein synthetic capacity and protein synthesis was found. At 24 hours after dosing the rats had increases in serum AST and ALP activity [18].

Beagle dogs, receiving single i.v. doses of 250-2000 mg/kg dexrazoxane, showed toxic signs during and after treatment including emesis, diarrhoea, anorexia, lethargy, weight loss and hypothermia. The lethal dose was 2000mg/kg dexrazoxane i.v. and the NOAEL dose was 250mg/kg. After 45 days recovery, there were no lesions in dogs given a 1000 mg/kg dose of dexrazoxane, showing that the acute lesions were reversible. Toxic effects were noted on rapidly dividing cells: bone marrow and gastrointestinal mucosa. Liver, kidney and intestinal toxicity were more severe at the highest dose and reduced or absent in lower doses.

- Repeat dose toxicity (with toxicokinetics)

The long-term toxicity of dexrazoxane was provided in rats and rabbits by i.v. route in compliance with GLP requirements and by literature in mice, dogs and swine.

Five daily intraperitoneal (i.p.) injections of 3000 mg/m^2/day did not produce toxicity in **mice**. Mice treated once weekly with 100 mg/kg i.p. for 8 weeks had slightly decreased weight gain.

In toxicity study rats were treated once daily i.v. with 5-200mg/kg/day dexrazoxane for 28 days followed by a 42-day recovery period or once in 14 days at 200 mg/kg dexrazoxane over 70 days . Decreases in body weight gain, spleen and testes weights, atrophy of lymph nodes, spleen, thymus and testes, decreased WBC and red blood cell (RBC) counts, and variable changes were observed. The NOAELs could not be established. In the 70 days arm of the study only male rats showed toxicity signs, particular a decrease in red blood cell parameters and testicular atrophy. In a 91 day toxicity study using up to 25 mg/kg/day dexrazoxane i.v., atrophie of lympoid tissue and tested, anaemia , depletion of WBC, high liver and low testicular and spleen weights were observed. The effects were dose related. In a satellite study to the 91 day study, rats received vehicle, dexrazoxane 5.0 mg/kg/day only, doxorubicin 0.25 mg/kg/day only, and 5.0 mg/kg/day dexrazoxane and 0.25 mg/kg/day doxorubicin for 91 days. Degeneration of the myocardium and sciatic nerve and glomerulonephropathy changes, which were seen in doxorubicin treated animals only, were less severe in the dexrazoxane and doxorubicin concomitant treatment group.

Administration of dexrazoxane 25 to 50 mg/kg i.p. once weekly for 12 weeks to male rats caused no changes in haematology and clinical chemistry examinations of rat blood samples, but a slight decrease in the rat's weight gain at 50 mg dexrazoxane/kg/week [19, 20]. Four doses of dexrazoxane 100 mg/kg over a 14-day period resulted in oxidative damage to the kidney in rats and an increase in lipid peroxidation markers [21]. Using immunohistochemical staining on tissue sections, comparable numbers of apoptotic cells in the kidney tubular cells or small intestinal epithelial cells were found in dexrazoxane-treated and saline-treated systemic hypertensive rats treated with the same once-weekly schedule for 12 weeks [22].

In systemic hypertensive (SHR) rats and WKY rats treated with 25 mg/kg dexrazoxane i.p. once weekly for 12 weeks, weight gain and blood pressure was affected one week after the last dose. Clinical chemical analysis and histopathology findings were unaffected by treatment. Male SHR rats given 25 mg/kg dexrazoxane i.p. once weekly for 12 weeks had the same number of various examined immune cells in the heart (dendritic cells, macrophages, t-helper and cytotoxic/suppressor t-lymphocytes) as controls.

Dexrazoxane was not tolerated by **rabbits** given 50 and 200 mg/kg/day i.v. as all animals were either found dead or were killed for humane reasons between days 9 and 22. As in rats, lymph nodes, thymus and testes were atrophic. The bone marrow was atrophic in both dexrazoxane-treated groups, and the high-dose group had bleeding in the lymph nodes and coecum lumen. Rabbits tolerated 12.5 and 25 mg/kg i.p. once weekly with three weeks interval five or six times without changes in haematology and clinical biochemistry values [1].

Beagle **dogs** were administered dexrazoxane using a slow constant-rate intravenous infusion of 3.8 - 4.9 ml/minute once daily for five consecutive days. Dexrazoxane doses of 250 and 500 mg/kg/day for five days were lethal to the dog. A nine day rest period between three series of five daily doses reduced toxicity and did not produce severe changes in serum liver function test. Dogs given dexrazoxane i.v. for 5 days tolerated up to 125 mg/kg/day with necroses and bleeding in lymph nodes and signs of liver and kidney affection. NOAEL was 15.6 mg/kg/day for 5 days treatment.

In dogs treatment every three weeks with doses of 25 mg/kg i.p. or 35 mg/kg i.v. dexrazoxane seven times were well tolerated [23, 24]. In addition, i.v. dose of 25 mg/kg dexrazoxane given up to 30 times in three week gaps, was well tolerated [25].
Swine tolerated a single dose of 12.5 mg/kg dexrazoxane i.p. every three weeks six times as for dogs [26].

- Genotoxicity

The mutagenic potential of dexrazoxane has been investigated *in vivo* in a micronucleus test in bone marrow cells of the mouse. Only this study was conducted under GLP conditions. Dexrazoxane (1000mg/kg) induced a statistically significant increase in the incidence of micronuclei in polychromatic erythrocytes (PCE) in both male and female mice.

Treatment with suspensions of dexrazoxane at single doses of 200 and 400 mg/kg i.p. increased the number of micronuclei in PCE in the bone marrow from male and female CCBF1 mice compared with solvent treated controls [27]. In bone marrow smears from male Chinese hamsters stained for metaphase chromosomes, an increase in the number of chromosome abnormalities compared with vehicle-treated control animals in the time interval of 12-48 hours after they were given an oral dose of 500 mg/kg razoxane was observed [27].

In vitro four salmonella strains were testes by Ames test with doses up to 5000 µg/plate razoxane. Raxozane was not mutagenic in this assay (McCann *et al.* 1975). An *in vitro* study performed with cytokinesis-blocked human lymphoblastoid cell line TK6 showed that 24-hour incubation of cells with dexrazoxane resulted in significantly increased numbers of micronuclei at 5 µM dexrazoxane concentrations and above [28].

- Carcinogenicity

No specific studies have been conducted with dexrazoxane in order to investigate the carcionogenic potential of the drug. In one study, withouth GLP compliant, 35 rats and mice were injected three times per week with up to 96 mg/kg razoxane (racemic product). The animals were dosed for 52 weeks, and then observed for a further 29-34 weeks. In female mice, the frequency of all haematopoietic neoplasms, was higher in the low-dose group ($P = 0.038$) and in the high-dose group ($P = 0.002$) than in the pooled controls and the incidence of uterine adenocarcinomas was higher in the low- and high-dose groups ($P<0.001$) than in the pooled controls (National Cancer Institute, 1978). Raxozane is determined to be carcinogenic in female rats and mice.

- Reproduction Toxicity

The applicant conducted no formal studies or published literature.
The results of one study investigating the prenatal effects of razoxane in mice, rats and rabbits administered orally have been provided (Duke, 1974). Growth retardation was seen in rat and mice foetuses when treatment was given on various days during early/mid gestation. Relatively low doses induced the resorptions, growth retardation and malformations. The frequency of malformations was below 10% in mice or rats.

- Local tolerance

The applicant has carried out a GLP-compliant local tolerance study in rabbits according to the CPMP/SWP/2145/00 Note for Guidance on Nonclinical Local Tolerance Testing of Medicinal Products. One i.v. injection per day for three days of dexrazoxane 3 mg/ml was injected into the lateral ear vein of rabbits (TTT 001). The animals were observed for 7 days following the last injection. There was no treatment related local tissue reaction.

- Other toxicity studies

Combination with anthracyclines

An overview of published studies investigating the toxicity of co-administration of dexrazoxane or razoxane and daunorubicin, doxorubicin or anti-cancer drugs has been provided.

Haematological toxicity of single doses of dexrazoxane and doxorubicin was studied *in vivo* in mice and *in vitro* in the colony forming unit granulocyte macrophage (CFU-GM) assay using human and murine granulocyte/macrophage precursor cells. Dexrazoxane (125 mg/kg i.p.) had no effect on CFU-GM survival after doxorubicin 10- 20 mg/kg i.v. exposure (Hofland et al 2005).

Dogs treated i.p. with 12.5 mg/kg dexrazoxane before 1 mg/kg doxorubicin i.v. 15 times at weekly intervals had decreased WBC and RBC counts and haemoglobin concentration compared with pre-treatment values. The dogs treated with dexrazoxane and doxorubicin did not have a larger decrease in the RBC and WBC counts compared with dogs treated with doxorubicin alone (Herman and Ferrans, 1983).

Pre-treatment with razoxane (200 mg/kg) prevented the acute lethality of a single high dose of 10 mg/kg daunorubicin in mice [29]. Dexrazoxane given i.p. in doses from 12,5 to 200 mg/kg protected against lethality in hamsters given 25 mg/kg daunorubicin i.v. [30].
Dexrazoxane protected against the epirubicin-induced cardiac and kidney toxicity in rats treated with weekly injections for 12 weeks [20]. Dexrazoxane reduced mitoxantrone-induced cardiotoxicity in rats [31].

Studies on impurities
No studies conducted.

Immunotoxicity
No studies conducted.

Ecotoxicity/environmental risk assessment
The drug product has been designated as an Orphan Drug in the European Union, and due to the Guideline (CHMP/SWP/4447/00) no environmental risk assessment has been performed.

Discussion on the non-clinical aspects

Pharmacology
Dexrazoxane, a detoxifying agent, reduced significantly the occurrence or size of skin wounds following daunorubicin, doxorubicin, epirubicin or idarubicin induced extravasation in mice. Skin wound area and size time-dependently increased with delayed dexrazoxane treatment. A triple treatment of 62.5 or 125 mg/kg dexrazoxane administered immediately, three hours and six hours after anthracycline administration was more effective than a single dose of 250 mg/kg. This daily treatment for 3 consecutive days is the rational for the clinical regimen (see SPC, section 4.2). If there is suspicion of extravasation by vesicant compounds other than anthracyclines through the same i.v. access, dexrazoxane would not be effective against the reaction from these compounds (see SPC, section 4.4).

Dexrazoxane reduces anthracycline cardiotoxicity and is approved in several countries for this indication. Dexrazoxane has anti-tumour properties.

In the safety pharmacology studies, due to the lack of toxicokinetic data, the appropriate dose level was difficult to assess. According to the ICH S7A guideline, in the absence of an adverse effect on the safety pharmacology parameters evaluated in the study, the highest tested dose should be a dose that produces moderate adverse effects. The used dose levels can be assessed as low from the fact that the single dose NOAEL in dogs is higher than the highest dose level used in the dog safety pharmacology study.

Pharmakokinetics
The metabolism of dexrazoxane as described in the dossier appears very simple, however it is unclear whether also other detoxification systems are active, and whether this implies a risk of interactions when co-medication with anthracyclines or other drugs relevant for the patient group takes place. Data on drug interaction between dexrazoxane and anthracycline has shown conflicting results. In the majority of non clinical and clinical studies, no effect was found. The studies in rats or humans, which found an effect of dexrazoxane on anthracycline pharmacokinetic were both characterized by the use of quite high anthracycline doses and showed an increase of anthracycline clearance.
Patients treated with anticoagulants should be monitored more frequently (see SPC, section 4.5). Dexrazoxane is generally not recommended in combination with live attenuated vaccines or with Phenytoin (see SPC, section 4.5). Detailed interactions are explained in section 4.5 of the SPC. Excessive immunosuppression with risk of lymphoproliferative diseases have to be taken into consideration when concomitant use of Ciclosporine or Tacrolimus is administered (see SPC, section 4.5). Due to an increase of occurrence of wounds, DMSO should not be used in patients that are administered dexrazoxane to treat anthracycline-induced extravasation (see SPC, section 4.4).

Toxicology
The main toxic effects for dexrazoxane, as expected for a topoisomerase 2 inhibitor which inhibits cell proliferation, were seen in proliferating tissues as haematologic and lympoid tissues and gastrointestinal mucosa. The kidneys and liver were also affected, being the main excretory organs for dexrazoxane and therefore containing high concentrations of the compound. No toxicokinetic studies have been performed by the applicant and therefore the animal: human exposure multiples cannot be calculated with confidence. Due to the provided conversion factors (Freireich et al) the animal doses expressed in mg/kg can be compared to human doses expressed in surface area (mg/m^2). The safety of dexrazoxane in humans is well described in the literature and the results from the clinical trials TT01 and TT02 showed acceptable safety results, with no reports of adverse reactions relating to cardiovascular and respiratory functions or the CNS. It is agreed that the clinical safety data suffice to waive the request for conventional toxicokinetic studies.

Dexrazoxane will be administered to patients undergoing cytotoxic therapy with anthracycline containing chemotherapy and its cytotoxic potential will therefore be added to that of the other chemotherapy administered (see SPC, section 4.4).

As dexrazoxane possess mutagenic activity, male patients should use contraceptives during treatment and for 3 months after treatment with dexrazoxane has been concluded (see SPC, section 4.6 and 4.4). Women of childbearing potential must use contraceptive measures during treatment (see SPC, section 4.4). Because of the potential for serious adverse reactions in nursing infants exposed to dexrazoxane, mothers should discontinue nursing during dexrazoxane therapy (see SPC, section 4.6).

Signs and symptoms of overdosage are likely to consist of leucopenia, thrombocytopenia, nausea, vomiting, diarrhoea, skin reactions and alopecia. Treatment should be symptomatic (see SPC, section 4.9).

4 Clinical aspects

Introduction
GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

The pharmacokinetics of dexrazoxane, given alone [32-35] and in combination with one or more other cytostatics agents [36-40] have been described in the literature (Table 1). No additional clinical pharmacokinetic studies were submitted by the applicant.

Table 1: Mean dexrazoxane pharmacokinetic parameters for an i.v. dose of 1000mg/m² dexrazoxane (Rosing et al [37])

	n	mean (SD)
$AUC_{0-\infty}$ (h.mg/l)	12	137 (49)
$T_{½ß}$ (h)	12	2.66 (1.54)
V_{dss} (l)	12	38.8 (7.9)
CL_{tot} (l/h)	12	13.8 (3.7)
CL_{ren} (l/h)	9	5.9 (1.2)
Urinary excretion (%)	9	42 (8)

- Absorption

No information on absorption following oral treatment was submitted.

- Distribution and Elimination

Five adult patients without hepatic or renal dysfunction received, in separate cycles, 1000 mg/m^2 i.v. infusion dexrazoxane over 30 min, 8 hours or 48 hours [32]. The kinetics of dexrazoxane in the serum followed a two-compartment open model. The mean peak serum levels for the three schedules were 75.3, 22.8 and 2.9 mg/ml, respectively. The mean T½ α values were 9.9, 10.6 and 19.5 minutes (mean 13.3 min) respectively, and the t½ β values 121.4, 143.6 and 173.0 minutes, respectively (mean 146 min). Total protein binding was less than 2%. The mean central compartment volume of distribution was 0.193 l/kg. Drug clearances for the 15 minutes and the 48-hour schedules were similar. Total urinary drug recovery was similar for the 3 schedules, on average 48% (range 25-62%). Less than 1% of dexrazoxane was excreted in the bile over 24 hours. In one patient with a creatinine clearance of 50 ml/min renal clearance was 23 % of total drug clearance *versus* a mean of 56% for all five patients and the serum level of dexrazoxane was increased. In two additional patients with malignant pleural effusions an equilibration with serum and identical decrease pattern was seen in one, while in the other the pleural concentration reached less than 50% of serum and disappeared more slowly.

In a phase I study, 46 paediatric patients received 2-hour infusions dexrazoxane daily for 3 days [33]. In 4 patients (9-16 years) receiving 3200-3800 mg/m^2 pharmacokinetic analysis demonstrated a mean α-half-life (t½ α =distribution half life) of 16 minutes and a β-half-life (t½ β = elimination half life) of 113 minutes. The volume of distribution was larger than in adults, but the difference was less apparent when normalized to body surface area rather than body weight. The 24-hour urinary excretion was 60% ± 24 %.

In a study conducted in 8 patients receiving 1 hour (2-5 h at the higher doses) infusions weekly of dexrazoxane 3.8 g/m^2 (5 patients), 5.9 and 7.4 g/m^2 (2 patients each), the biphasic elimination curve had a t½ α of 1.0 ±0.3 h and a t½ β of 3.2 ± 0.9 h. Mean clearance was 288.7 ± 85 ml/h/kg and the apparent Vd was 1.3 ± 0.4 l/kg. The mean percentage of total dose recovered in the urine was 33.7 % in 24 h. In one patient, the ratio of pleural fluid to plasma concentration at the end of infusion was 0.1[34].

Inter-individual variability was evaluated from pharmacokinetic data collected in 19 patients treated with i.v. infusion of dexrazoxane over 30 min to 2 hours [32-34]. The average coefficient of variation was 38.3% and 24.0 % for the $t_{½}α$ and the $t_{½}β$, respectively. The coefficient of variation was 30.4%, and 35.6% for total clearance and the volume of distribution, respectively. The intra-individual variability was investigated in 5 patients receiving i.v. infusion of 1000 mg/m^2 of dexrazoxane within various schedules 30 min, 8 hour and 48 hour. The average coefficient of variation was 44.7%, 17.7%, 13.6%, 14.9% and 38.0% for $t_{½}α$, $t_{½}β$, total clearance, AUC and Volume of distribution, respectively [32].

In a study conducted in 21 patients treated by 96-hour continuous infusion in a dose-escalation phase I study with doses from 125 mg/m^2/d to 250 mg/m^2/d [35], the mean steady state clearance was 7.2 l/h/m^2 and the t½ β was 2.0 h ± 0.8 h. The mean percentage of administered drug recovered in the urine at steady state was 40.5%.

- Metabolism

Dexrazoxane underwent *in vivo* a rapid hydrolysis by the enzyme dihydropyrimidine aminohydrolase (DHPase) to its two one-ring opened metabolites [40]. DHPase is found in liver cells and in renal cells. Both intermediate one-ring opened metabolites are subsequently converted by the enzyme dihydroorotase (DHO), to the two-ring opened metabolite ADR-925. DHO is found in a number of cells including heart, liver, kidney and blood cells. ADR-925 has a structure similar to EDTA and is a strong metal chelator for iron (free and bound), copper and other metals. The two one-ring opened hydrolysis products appeared quickly in plasma at low levels upon completion of dexrazoxane infusion and then rapidly decreased with half-lives of 0.6 and 2.5 hours. The two-ring opened ADR-925 was detectable at the end of the dexrazoxane infusion, then rapidly increased three-fold at 15 min after the infusion, remained constant for 4 hours and then decreased to about half at 24 hours.

- Dose proportionality and time dependencies

The concentration at steady state of dexrazoxane (following continuous infusion) was achieved within the first 12 hours of infusion [35]. Upon completion of the infusion, plasma dexrazoxane concentrations declined rapidly in a mono-exponential form and were undetectable within 12-24 hours. AUCs were dose-proportional [34, 36]. The systemic clearance and volume of distribution were found to be independent of dose.

- Special populations

No studies in special populations or investigating intrinsic factors were submitted.

- Pharmacokinetic interaction studies

Pharmacokinetic data available from the literature, in which dexrazoxane was administered with anthracyclines, were submitted. The dose of dexrazoxane (escalating doses from 60 to 900 mg/m² combined with 60 mg/m^2 of doxorubicin) had no influence on doxorubicin pharmacokinetics [36]. Dexrazoxane did not influence epirubicin pharmacokinetics and escalating doses of epirubicin did not significantly alter the pharmacokinetics of dexrazoxane [38]. A 30% increase in terminal half-life and a decrease in total body clearance were observed when the epirubicin dose was raised from 60 to 100 mg/m^2. High doses of dexrazoxane (900 and 1200 mg/m^2) increased the systemic clearance of epirubicin, resulting in a decrease in the AUC [39]. Elimination half-life, Cmax and volume of distribution of epirubicin were not affected. Interaction studies of dexrazoxane, etoposide and methylprednisolone have also been described [40].

Pharmacodynamics

- Mechanism of action

Two main modes of action described for dexrazoxane consist of metal ion chelation [41] and topoisomerase II inhibition [Tanabe et al 42]. The precise pharmacodynamic mechanism is not known. Human primary pharmacodynamic studies have not been submitted.

- Primary and secondary pharmacology

No studies in the claimed indication have been submitted. The secondary pharmacology of dexrazoxane, used as anticancer agent and not for the treatment of anthracycline extravasation, was investigated through six phase 1 trials in adults [33-35, 43-45] and in on study in children [46] (table 2).

Table 2: Summary of safety and MTD results from phase 1 studies of dexrazoxane

Authors	**Administration**	**Dose levels**	**Dose-limiting toxicity**	**MTD and recommended dose for phase II trials**
Vogel et al, 1987 [34]	1-hour i.v. infusion (prolonged to 2-5 h at the highest doses)	3800-7400 mg/m^2/d once weekly	hepatotoxicity in "good risk" pts granulocytopenia in heavily pretreated pts. .	7400 mg/m^2 /wk in "good risk" patients 3800 mg/m^2 /wk in heavily pretreated patients
Holcenberg et al 1986 [33]	2-hour i.v. infusion	500-4000 mg/m^2 /d x 3	liver toxicity (SGOT, bilirubin, coagulation factors)	3500 mg/m^2/d x 3
Von Hoff et al 1981 [43]	'short' i.v. infusion	500-1500 mg/m^2/d x 3 q 3 wk	leukopenia and thrombocytopenia	1250 mg/m^2/d x 3 for patients with no prior nitrosourea 1000 mg/m^2 for pts with prior nitrosourea
Liesmann et al 1981 [44]	15-min i.v. infusion	200-1500 mg/m^2/d x 5 q 3 wk	granulocytopenia	1250 mg/m^2/d x 5 for "good risk" patients 800 mg/m^2/d x 5 for heavily pretreated patients
Koeller et al 1981 [45]	48-hour continuous i.v. infusion	100-500 mg/m^2/d for 48 hours q 3 wk	granulocytopenia	500 mg/m^2/d/48 hours (1000 mg/m^2/48 hours)
Tetef et al 2001 [35]	96-hour continuous i.v. infusion	125-250 mg/m^2/dx4 (96 hours)	thrombocytopenia nausea/vomiting diarrhoea	166.25 mg/m^2/d for 96 hours
Hochster et al 1992 [36]	15 min i.v. infusion beginning 30 minutes before doxorubicin treatment	60-900 mg/m2 per day in three week cykles	leukopenia neutropenia	600 mg/m^2 be given with single-agent doxorubicin at a dose of 60 mg/m^2

Abbreviations: MTD: maximum tolerated dose; i.v.: intravenous, SGTO: Serum glutamic-oxaloacetic (glutamate-oxaloacetate) transaminase

The maximally tolerated dose (MTD) was generally determined by the occurrence of reversible bone marrow toxicity (especially granulocytopenia) and reversible hepatotoxicity (SGOT) and bilirubin elevation while other toxicities were mild and not dose-limiting. The MTD was influenced by age, the extensiveness of prior treatment, the schedule and was lower with continuous infusion as compared to short bolus. In phase 1 studies, the metal ion excretion was examined [33, 35, 43]. Iron and calcium serum was increased and a zinc serum was decreased. Iron and zinc urinary excretion was increased and no change in magnesium, calcium, copper irons was observed.

Discussion on clinical pharmacology

The description of pharmacokinetics of dexrazoxane was based on bibliographic data retrieved from the literature. Overall, these studies provide sufficient level of detail and further studies are considered unnecessary. However, there were insufficient data about intrinsic pharmacokinetic factors such as age, gender, race and weight. Inter-and intra-individual pharmacokinetic variabilities have not been studied systematically. Based on a limited number of patients, inter-individual variability calculated as the coefficient of variation (CV %), was estimated to be approximately 30% for the main pharmacokinetic parameters (see SPC, section 5.2). No information was provided about pharmacokinetic interaction with other medicinal products specific to dexrazoxane.
Human primary pharmacodynamic studies have not been conducted. The chelating property is probably responsible for an increased urinary excretion of iron and zinc and a decreased serum concentration of calcium as described in a few studies (see SPC, section 5.1).

Clinical efficacy
The clinical programme for Dexrazoxane included two open uncontrolled studies. These studies, conducted according to GCP, were designed on the basis of the non-clinical work and on the observation of a number of pilot cases.

- Dose response study

No dose-response studies were conducted. In both pivotal studies, the dosage regimen was the same and based on the published and unpublished non-clinical and clinical work in other indications.

- Main study(ies)

Study TT01

The study was a prospective, open-label, single-arm, multicentre clinical trial.

METHODS

Study Participants
Main inclusion criteria were patients with cancer treated with anthracycline, history of anthracycline extravasation <6 hours confirmed by fluorescence microscopy by the local pathologist, presence of at least one of the symptoms (pain, swelling, redness), performance status < 2 and age >18 years The main exclusion criteria were known allergy towards dexrazoxane, reasonable suspicion of extravasation by other compounds than anthracycline, 3 × upper normal level of ASAT, ALAT, LDH, bilirubin and alkaline phosphatase. Pregnant women or women of childbearing age and potential not using an efficient contraceptive were not eligible.

Treatments

Treatment with dexrazoxane 1000 mg/m^2 as i.v. infusion over 1-2 hours was started within 6 hours from the incident and was repeated after 24 hours (1000 mg/m^2) and 48 hours (500 mg/m^2) in all patients. The maximal dose of dexrazoxane that could be given was 2000 mg. No other dose modification was allowed.

Objectives

The primary objective was to avoid surgical intervention following the accidental extravasation of anthracycline drug, thus preventing the patient from sequelae. Secondary objectives were: to avoid any deleterious postponement of the cancer treatment itself; to describe and evaluate subjective and objective symptoms and the clinical progression in the damaged area following treatment with dexrazoxane; and to evaluate the tolerance to and/or toxicity of dexrazoxane used for this indication according to the indicated schedule.

Outcomes/endpoints

The primary endpoint was the proportion of patients undergoing surgical intervention. Both the plastic surgeon/surgeon and the oncologist/haematologist evaluated any sign of progression in the area of extravasation. Development of blistering and manifest necrosis defined progression requiring surgical intervention. The extent and number of blistering and necrotic areas were registered before operation, and a colour photograph taken. Secondary endpoints were the development of sequelae in the form of sensory disturbances, skin atrophy, pain and limitation of movements. The study data were reviewed by an Independent Review Committee.

Sample size

The sample-size calculation was based on the hypothesis of a proportion of surgical interventions of 20% or less. The original planned number of patients was 25.

Randomisation

The study was non-randomised.

Blinding (masking)

The study was an open study.

Statistical methods

The proportion of surgical interventions was estimated using exact binomial 95% confidence intervals. An interim analysis was scheduled be performed after inclusion of the first 5 patients. The trial management team would discuss the future of the trial, should it have been necessary to operate on 3 of these 5 patients. A second interim analysis was planned after the inclusion of the 17th patient. If none of the 17 patients have been operated upon (0%, 95% CI 0–19.5), the trial management would discuss the future of the trial. At the completion of the 18th patient, who were eligible for efficacy evaluation, no failures had occurred, and the inclusion of patients was stopped (recruitment to the study was stopped when 18/23 evaluable patients had been entered).

RESULTS

Participant flow

23 patients were entered and received treatment with dexrazoxane. Eighteen were evaluable for efficacy and safety and a further five patients were evaluable for toxicity only. Of these, four had negative biopsies and received no further therapy. One patient had extravasation in a CVAD not suitable for obtaining surgical biopsies, but received the full three-day treatment. Of the 18 evaluable patients, 17 received dexrazoxane day 0, 1, and 2. One patient received dexrazoxane on day 0 and 1 only. Sixteen patients were followed for three months. Two patients completed the day 28-visit, but died of their primary cancer diseases before the 3-month visits.

Recruitment

Patients were recruited by 10 centres in Denmark from July 2001 to June 2003.

Conduct of the study

No major protocol amendments were made.
Baseline data

Baseline characteristics for patients evaluable for efficacy or toxicity, are tabulated in Table 3.

Table 3. Baseline characteristics (study TT01) for patients evaluable for efficacy, for those evaluable for toxicity only, and for both groups.

		Patients evaluable for efficacy and toxicity (n=18)	Patients evaluable for toxicity only (n=5)	All patients (n=23)
Sex	Female/Male	13/5	5/0	18/5
	%	72/28	100/0	78/22
PS (ECOG)	0/1/2	12/4/2	4/0/1	16/4/3
	%	67/22/11	800/20	70/17/13
EV-location	Hand/Forearm/CVAD	7/11/0	1/3/1	8/14/1
	%	39/61/0	20/60/20	35/61/4
Anthracycline	Doxorubicin/Epirubicin	7/11	2/3	9/14
	%	39/61	40/60	39/61
EV at cycle	1-3/4-6/≥7	9/3/6	5/0/0	14/3/6
	%	50/17/33	100/0/0	61/13/26
Acute local Tx	Aspiration	7	1	8
	Aspiration + ice/cold compress	5	2	7
	Aspiration + heat	1	0	1
	Ice/cold compress	3	2	5
	Compression	1	0	1
	None	1	0	1
Cancer types	Breast cancer	10	3	13
	Lymphoma	7	0	7
	Gastric cancer	1	0	1
	Myeloma	0	1	1
	Ewing's sarcoma	0	1	1
Time to Topotect	Mean/median/range (minutes)	238/248/115-355	224/230/145-295	235/235/ 115-355
Age	Mean/median/range (years)	56.6/54.5/41-76	49.2/43/40-68	55.0/53/ 40-76
Baseline signs and symptoms	Swelling	16 (89%)	N/A	N/A
	Redness	14 (78%)		
	Pain	7 (39%)		
	Blisters	2 (11%)		
	Dysesthesia	1 (6%)		
	None	0 (0%)		
Number of signs and symptoms	1/2/3/4/None	3/9/5/1/0	N/A	N/A
	%	17/50/28/6/0		
Size of affected area at baseline	Mean/median/range (cm^2)	23,6/16/1-75 (N=22 as CVAD patient has affected area of 0 x 0 cm)	17,9/9,75/2,16-50 (N=4 as CVAD patient has affected area of 0 x 0 cm))	22.5/16/ 1-75
Estimated amount of anthracycline in catheter before the EV accident	Epirubicin treated pts mean/median/range (%)	76/100/10-100	N/A	N/A
	Doxorubicin treated pts mean/median/range (%)	59/50/20-100		
Other Tx in same i.v. access before anthracycline	No/Yes	10/8	0/5	10/13
	%	56/44	0/100	43/57

Abbreviations: PS (ECOG): Performance status according to the ECOG scale; EV: Extravasation; CVAD: Central venous access device; Mo/Tu…/Su: Weekdays; Tx: Treatment; Min: Minutes; i.v.: Intravenous

Numbers analysed

All 18 patients evaluable for efficacy had at least three biopsies from the affected area of which at least one was fluorescence positive. All biopsies were obtained within the time limit of 24 h. From 15 of 18 patients (83%) four or more biopsies were obtained. Nine of 18 (50%) patients had 4 or more fluorescence positive biopsies.

Outcomes and estimation

None of 18 evaluable patients with biopsy-verified (fluorescence-positive) anthracycline extravasation underwent surgical intervention (95% CI 0-18.5%). Seventeen of 18 patients (94.4%) did not develop necrosis. One patient (5.6%) developed an infection in the biopsy area that led to a small necrosis that gradually healed upon treatment of the infection with antibiotics. Two patients had blisters in the affected area *at baseline*. In both cases the blistering had disappeared at follow-up 8-12 hours after the first treatment. No patients developed blistering after treatment with dexrazoxane.
Concerning the long-term sequelae (three months follow up), 16/18 patients (88.9%) had no sensory disturbances, 18/18 (100%) had no limitations of movement, 17/18 (94.4%) had no skin atrophy, and 17/18 patients (94.4%) had no pain at the last follow-up.

Twelve patients (67%) continued their scheduled further chemotherapy course(s) without delay after the EV incident. Six patients (33%) experienced delay in the planned cytotoxic treatment. Nine patients (50%) were admitted to the hospital due to the EV with a mean duration for the 9 patients of 3.3 days (range 1-6 days; median 3 days).

Ancillary analyses

Not applicable.

Study TT02

The study was an open, single-arm multicentre phase 2-3 trial.

METHODS

Study Participants

The inclusion and exclusion criteria were the same as in TT01, and TT02 additionally excluded patients who had topical use of DMSO at the area of the accident and who had received dexrazoxane within the last 3 weeks. At least two skin biopsies (punch- or knife-biopsies) were required to confirm the anthracycline extravasation. The biopsies were performed under local analgesia, which was applied outside the area of redness and swelling. The biopsies were not to contain any part of the vein used for the infusion. They were to be ≥ 6 mm in length and ≥ 6 mm in width. The tissue was to be frozen at –20 to –80 °C. All biopsies were analysed in a central pathology department. Each biopsy was assessed as fluorescence-positive or as fluorescence-negative. Only those patients with fluorescence-positive microscopy were evaluable for efficacy.

Treatments

See treatments for trial TT01.

Objectives

The primary objective was to avoid surgical intervention following the accidental extravasation of anthracycline drug, thus preventing the patient from sequelae.

Outcomes/endpoints

The primary endpoint was the proportion of patients undergoing surgical intervention.
Secondary efficacy parameters included the development of necrosis (verified by two independent physicians), the development of late sequelae (verified by two independent physicians) in the form of impaired limb function, disfigurement, pain and neurological deficit, and the postponement of the scheduled cancer treatment due to treatment of the extravasation incident.

Sample size

The sample-size calculation was based on the hypothesis of a 70% reduction in the proportion of surgical interventions, from a reference value of 35% (based on the literature) to 10% (alpha =.025, beta = .20, using a one-sided exact binomial test). A sample size of 35 patients was calculated, taking into account loss to follow-up.

Randomisation

The study was non-randomised.

Blinding (masking)

The study was an open study.

Statistical methods

The exact binomial test was used. The proportion of surgical interventions was estimated using exact binomial 95% confidence intervals.
The protocol (amendment) specified that an interim analysis was to be conducted after inclusion of the first 18 patients – solely for the purpose of evaluating side effects of the dexrazoxane treatment.
An initial interim analysis was conducted and reported on the basis of the first 19 patients entered, as one patient was incorrectly included. A second interim analysis was based on data from the first 46 patients entered.

RESULTS

Participant flow

57 patients entered the study at 24 centres and received the first dose of dexrazoxane. One of these patients was entered twice as she experienced extravasation on two occasions, once in each arm. Of the 57 patients entered, 36 were evaluable for efficacy. Nine patients had negative biopsies and 12 patients had major protocol deviations. The protocol deviation for four patients was no biopsy. All 57 patients enrolled received study treatment and therefore were included in the safety population.

Recruitment

Patients were recruited by 24 centres in Denmark, Italy, Netherlands and Germany form July 2002 to August 2005.

Conduct of the study

The final protocol was dated 26 November 2001 and one amendment was issued (26 September 2002). This amendment incorporated several changes to the protocol including a change of the objectives, which led to a change in the Success Criteria **from** 'the absence of surgical intervention and postponement of the planned antineoplastic treatment of the patient' **to** 'the prevention of surgical intervention, necrosis and late sequelae evaluated 3 months after the extravasation'.

Amendment 1 also modified the sample size calculation : 35 evaluable patients rather than 55 were to be recruited.

Baseline data

Baseline characteristics for patients evaluable for efficacy or safety are shown in Table 4.

Table 4. Baseline characteristics (study TT02)

		Patients evaluable for efficacy (n=36)	Patients evaluable for safety (n=57)
Sex	Female/Male	24/12	40/17
	%	66.7/33.3%	70.2/29.8%
PS (ECOG)	0/1/2	27/8/1	39/15/3
	%	75.0/22.2/2.8%	68.4/26.3/5.3%
Anthracycline	Doxorubicin/Epirubicin/others	16/20	24/31/2
	%	44.4/55.6%	42.1/54.4/3.6%
EV at cycle	1-3/4-6/≥7	22/8/6	33/14/10
	%	61.1/22.3/16.7%	58/24.6/17.5%
Cancer types	Breast cancer	17(47.2%)	27(47.4%)
	Lymphoma	14(38.9%)	16(28.1%)
	Myelomatosis	1(2.8%)	3(5.3%)
	Ovarian cancer	1 (2.8%)	2(3.5%)
	others	3 (8.3%)	9(15.9%)
Age	Mean/SD/range (years)	55.1/13.1/34-81	55.5/13.5/21-92
Baseline signs and symptoms	Swelling	29 (80.6%)	42(73.7%)
	Redness	28(77.8%)	48(84.2%)
	Pain (mild/moderate)	13(36.1%)/3(8.3%)	23(40.4%)/5(8.8%)
	Blisters	0	1 (1.8%)
	Dysesthesia	1(2.8%)	2(3.5%)
	Limitation of movements	3(8.3%)	3(5.3%)
Biopsies	Total/pos/neg	88/68/19	117/76/39
	Median of total/pos/neg	2/2/0	2/2/1
Size of affected area at baseline	Mean/median/range (cm^2)	39/25.4/1.0-253	47.1/30.5/1.0-253.0

Numbers analysed

All 57 patients enrolled received study treatment and therefore were included in the safety population. 36 Patients were evaluable for the efficacy analysis. Twenty-one patients were excluded from this analysis. Nine patients had negative biopsies and 12 patients had major protocol deviations. The protocol deviation for four patients was no biopsy. All patients in the efficacy population had at least one positive biopsy (by definition). The median number of biopsies analysed per patient was 2 in both the safety population and the efficacy population.

Outcomes and estimation

One patient (2.8%) in the efficacy population underwent surgery as a consequence of the extravasation incident ($p<0.0001$; 95%CI 0.1%-14.5%). The patient had progressive symptoms, including necrosis, and underwent surgery to remove the necrotic tissue on Day 13 and again 3 days later. Two other patients in the efficacy population also had necrosis during the study, but this was due to the biopsy and not extravasation. Ten patients (27.8%) in the efficacy population experienced a postponement of scheduled chemotherapy. For one patient, there was no duration of postponement reported as no further chemotherapy was given because of surgery. The duration of postponement was 7 to 15 days (mean 10 days) for the nine patients for whom a duration was reported.

A summary of sequelae present at the last follow-up visit for the efficacy population is shown in Table 5 for an initial series of 29 patients.

Table 5. Summary of sequelae present at the last follow-up visit for the efficacy population.

	Efficacy population (n=29)
At least one sequela	13 (36.1%)
Sensory disturbances	7 (19.4%)
Skin atrophy	4 (11.1%)
Pain	9 (25.0%)
Disfigurement	1 (32.8%)
Limitation of movement	3 (8.3%)
No sequelae	23 (63.9%)

Ancillary analyses

None performed.

- Analysis performed across trials (pooled analyses and meta-analysis).

None performed.

- Clinical studies in special populations

Clinical studies in patients with renal and/or hepatic impairment have not been performed.

- Supportive studies

A review of the literature was presented. Two patients with large extravasation of epirubicin and doxorubicin, both receiving dexrazoxane for 3 days (1000,1000 and 500mg/m² on day 1-3, respectively), did not need surgical intervention and no sequelae were observed [47]. A third patient, with a large biopsy-proven epirubicin extravasation, received the same treatment and also recovered without ulceration and sequelae except dysaesthesia [48]. One patient with an epirubicin extravasation [49] on the hand was treated first with DMSO for 20 minutes, cooling and hydrocortisone ointment and subsequently, after 12 hours, with a single dose of dexrazoxane (administered i.v.). The lesion healed slowly over 4 months without surgery. To one patient with a large doxorubicin extravasation in the chest wall from a needle displacement of a Port-a-Cath entrance, DMSO was applied every 6 hours for 18 hours (stopped due to local irritation), and dexrazoxane 1500 mg was administered i.v. within one hour and repeated after 5 hours and the next day [50]. The wound where the chamber was placed healed without delay but 3 months later a necrosis developed at the site, which then needed surgery. The authors concluded that the 3 days of dexrazoxane prevented the immediate toxic effect of the extravasation but that additional dexrazoxane probably should have been given to prevent the delayed tissue necrosis

- Discussion on clinical efficacy

The demonstration of the clinical efficacy of dexrazoxane for the treatment of anthracycline extravasation is based on the results of two multicentre, open label, single-arm studies, using an external control from the literature. In total 1 out of 54 patients evaluable for efficacy had necrosis that required surgical treatment as a consequence of the extravasation. Both pivotal studies reached the primary criterion and statistical requirements. Efficacy has been demonstrated whichever the reference chosen (surgery in 100% as in TT01 with reference to the Danish standard, or 35% as in TT02 with reference to literature). The effect observed can be considered as a clear clinically benefit.

One single dose level and dose schedule was assessed. It was not possible to individualise the dose of dexrazoxane in relation to the amount of extravasated anthracycline. The recommended schedule of the treatment is based on literature and no experience with modification is available. Until more knowledge is obtained, the 6-hour time interval between the proof of an anthracycline extravasation and the administration of Savene is recommended (see section 4.2 of the SPC).

Only one patient with extravasation in a CVAD was included. Section 5.1 in the SPC mentions that the efficacy of Savene has not been investigated in a sufficient number of patients with suspicion of anthracycline extravasation from a central venous access device.

Patients with neutropenia and thrombocytopenia > CTC grade 1 have not been included in the clinical studies. This patient group is expected to be most vulnerable regarding hematological toxicity. The safety of dexrazoxane in this patient group remains unclear and has to be followed thoroughly by the applicant. It is also mentioned in section 4.4 of the SPC.

Since studies on special populations were not conducted, dexrazoxane is not recommended for treatment (see section 4.2 of the SPC). In case of hepatic impairment a routine liver function test is recommended before each administration of dexrazoxane (see section 4.4 of the SPC).

Since biopsy is not available in all centres and none of the patients excluded form the efficacy analyses due to a negative biopsy required surgical intervention, the indication of dexrazoxane can include patients in whom biopsy is not feasible.

Clinical safety
Safety data was collected in two open uncontrolled studies (TT01, TT02). Adverse events were monitored up to day 28. Adverse events were graded in severity by the investigator according to NCI-CTC criteria and causality assessments provided. The clinical adverse events are also coded according to MedDRA. Laboratory test results were assigned a grade by the applicant, according to the NCI-CTC definitions.

- Patient exposure

Data from 80 patients who received at least one dose of dexrazoxane have been included. For all patients the scheduled regimen was an initial dose of 1000 mg/m^2, followed 24 hours later by a further dose of 1000 mg/m^2 and after a further 24 hours by a dose of 500 mg/m^2. In total 80 (100%) patients received dexrazoxane treatment on Day 1, 72 (90%)patients on Day 2 and 69 (86.2%) patients received the treatment on Day 3 (Table 6) .

Table 6. Exposure to dexrazoxane in TT01 and TT02

	TT01 (N = 23)	TT02 N=46
Day 1	23 (100%)	57 (100%)
Day 2	19 (82.6%)	53 (92.98%)
Day 3	18 (78.3%)	51 (89.47%)
Day 4	0	1 (1.75%)
Day 5	0	1 (1.75%)

In study TT01, four patients received only one dose of dexrazoxane as they had negative biopsies and so received no further treatment. One additional patient had a traumatic femoral bone fracture and did not receive the last dose of dexrazoxane.

In study TT02 four patients received treatment on Day 1 only because their biopsies were investigated at the local hospital and found to be fluorescence negative. Two patients received treatment on Days 1 and 2 only; one withdrew because of personal reasons, while one stopped treatment because of adverse events (see below). One patient received five dexrazoxane treatments over Days 1 to 5 as (because of cooling of the affected area) it was considered that the amount reaching the affected area would be reduced. Treatments on Days 4 and 5 were at the same dosage as given on Day 3.

- Adverse events

The incidence of adverse reactions in studies TT01 and TT02 that are related or possibly related to treatment are shown in Table 7. All patients in TT01 and the great majority in TT02 experienced one or more adverse events.

In TT01, the most common adverse events were those in the general disorders and administration site conditions, affecting 20 (87.0%) patients. The most frequently reported adverse events in this system organ class (SOC) were injection site pain (9 patients, 39.1%), pyrexia (6 patients, 26.1%) and injection site phlebitis (5 patients, 39.1%) followed by peripheral oedema (4 patients, 17.4%) and fatigue (3 patients, 13.0%). Adverse events of the gastrointestinal disorders SOC were also common (15 patients, 65.2%), with the most common individual adverse event nausea (13 patients, 56.3%). Infections and infestations were reported for eight (34.8%) of study participants.

The adverse event profile in TT02 was similar to that in TT01. In the safety population, 45 (78.9%) patients had at least one clinical adverse event and 27 (47.4%) patients had at least one treatment-related clinical adverse event. SAEs were reported for 20 patients (35.1%), with SAEs classed as having a 'suspected' or, in two cases, probable, relationship to study medication in nine patients (15.8%). The most common adverse events were those in the gastrointestinal disorders SOC (29 patients, 50.9%), with the most common individual adverse event nausea (36.8% of patients). General disorders and administration site conditions were also common, affecting 45.6% of patients, but were less common than in TT01. The most frequently reported adverse events in this SOC were fatigue (12.3%) and pyrexia (19.3%). Infections and infestations were reported for 28.1% of study participants.

Table 7. Incidence of adverse reactions in studies TT01 and TT02 that are related or possible related to treatment.

System Organ Classes (SOC)	Frequency	Preferred Terms (PT)	All grades	Grade 3	Grade 4	Grade 3+4
Gastrointestinal disorders	Very common	Nausea	15 (18.8%)	0 (0%)	0 (0%)	0 (0%)
	Common	Vomiting	6 (7.5%)	0 (0%)	0 (0%)	0 (0%)
		Diarrhoea	3 (3.8%)	1 (1.3%)	0 (0%)	1 (1.3%)
		Stomatitis	2 (2.5%)	2 (2.5%)	0 (0%)	2 (2.5%)
		Dry mouth	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions	Very common	Injection site pain	13 (16.3%)	1 (1.3%)	0 (0%)	1 (1.3%)
		Pyrexia	6 (7.5%)	2 (2.5%)	0 (0%)	2 (2.5%)
		Injection site phlebitis	5 (6.3%)	0 (0%)	0 (0%)	0 (0%)
		Injection site erythema	3 (3.8%)	0 (0%)	0 (0%)	0 (0%)
		Fatigue	2 (2.5%)	0 (0%)	0 (0%)	0 (0%)
		Injection site induration	2 (2.5%)	0 (0%)	0 (0%)	0 (0%)
		Injection site swelling	2 (2.5%)	0 (0%)	0 (0%)	0 (0%)
		Oedema peripheral	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
		Somnolence	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	Very common	Postoperative infection	8 (10.0%)	3 (3.8%)	0 (0%)	3 (3.8%)
	Common	Infection	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
		Neutropenic infection	1 (1.3%)	1 (1.3%)	0 (0%)	1 (1.3%)

System Organ Classes (SOC)	Frequency	Preferred Terms (PT)	All grades	Grade 3	Grade 4	Grade 3+4
Injury, poisoning and procedural complications	Common	Wound complication	3 (3.8%)	0 (0%)	0 (0%)	0 (0%)
Investigations	Common	Weight decreased	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders	Common	Decreased appetite	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	Common	Myalgia	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	Common	Dizziness	2 (2.5%)	1 (1.3%)	0 (0%)	1 (1.3%)
		Sensory loss	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
		Syncope	1 (1.3%)	1 (1.3%)	0 (0%)	1 (1.3%)
		Tremor	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	Common	Vaginal haemorrhage	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
		Pneumonia	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	Common	Alopecia	5 (6.3%)	0 (0%)	0 (0%)	0 (0%)
		Pruritus	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	Common	Phlebitis	2 (2.5%)	0 (0%)	0 (0%)	0 (0%)
		Thrombophlebitis superficial	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
		Venous thrombosis limb	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)

Very common: >1/10, common >1/100 to <1/10, n=80

The grade 3 stomatitis was reported for a patient who entered one study twice and was reported under both exposures.

- Serious adverse event/deaths/other significant events

In study TT01, there were two deaths: two patients died of the primary malignant disease before the 3-month visit. In TT02 three SAEs resulted in death. One patient, who received five doses of dexrazoxane, experienced septic shock due to neutropenia fever 4.5 months after the extravasation, one patient experienced respiratory insufficiency due to *Aspergillus* infection 2.5 months after the extravasation, and one patient experienced pneumonia 2 months after the extravasation. All deaths were considered unrelated to study medication and all three received the next course of chemotherapy after the extravasation and before death.

In TT01, 12 SAEs were reported for seven different patients (four patients had more than one SAE reported). Eight events in four patients were related to dexrazoxane. Two were related to local injection site reactions and two events were related to neutropenia/neutropenic fever/infection. In TT02 twenty patients experienced SAEs, with nine patients experiencing SAEs with suspected relationship or, in two cases, a probable relationship to treatment; none had a definite relationship. Two of the events with a suspected relationship were the stomatitis in the patient treated twice, six were related to fever/infection and one to somnolence/dizziness.

- Laboratory findings

The laboratory test-based toxicities (according to NCI CTC definitions) combined for the two studies are summarised in Table 8. Grade 2-4 toxicities were very common for white cells, neutrophils, platelets, haemoglobin, ASAT and ALAT.

Table 8. Incidence of laboratory abnormalities in TT01 and TT02

	No of pts with post baseline	CTC grade 3		CTC grade 4		CTC grade 3-4	
Lab test	**value**	**N**	**%**	**N**	**%**	**N**	**%**
Haemoglobin	80	2	2.5%	0	0.0%	2	2.5%
WBC	80	20	25.0%	16	20.0%	36	45.0%
Neutrophils	78	17	21.8%	19	24.4%	36	46.2%
Platelets	80	17	21.3%	0	0.0%	17	21.3%
Sodium (Hypo)	79	4	5.1%	1	1.3%	5	6.3%
Potassium (Hypo)	79	2	2.5%	0	0.0%	2	2.5%
Potassium (Hyper)	79	0	0.0%	0	0.0%	0	0.0%
Alkaline Phosphatase	77	0	0.0%	0	0.0%	0	0.0%
Bilirubin	77	1	1.3%	0	0.0%	1	1.3%
ASAT (SGOT)	57	1	1.8%	1	1.8%	2	3.5%
ALAT	71	1	1.4%	2	2.5%	3	3.9%
Creatinine	76	1	1.3%	1	1.3%	2	2.6%
LDH	78	0	0.0%	0	0.0%	0	0.0%
Calcium Total (Hypo)	28	1	3.6%	1	3.6%	2	7.1%

The most commonly observed CTC was decreased white cell count (71.9% of patients) with decreased neutrophil count also being very common (59.6% of patients). Decreased haemoglobin, thrombocytopenia, increased ALAT and increased ASAT were also frequently found. The most common grade 4 toxicities were decreased white cell and neutrophil counts. However, grade 4 toxicities were also found for ASAT and ALAT as well as isolated cases of increased and decreased total calcium decreased sodium and increased creatinine.

- Safety in special populations

No analysis of safety in special populations was performed due the low patient numbers.

- Safety related to drug-drug interactions and other interactions

No drug-drug interaction was investigated.

- Discontinuation due to adverse events

One patient in TT01 had treatment discontinued because of an adverse event, which was unrelated to dexrazoxane. One patient in TT02 had treatment discontinued because of an adverse event. The patient experienced a serious adverse event during the first infusion (dizziness and progressive somnolence) and had a recurrence of symptoms at the end of the second infusion and was withdrawn from further treatment.

- Post marketing experience

At the time of the assessment, dexrazoxane had not been marketed elsewhere for the indication applied for.

- Discussion on clinical safety

Safety data from 80 patients treated with dexrazoxane were provided from two non-comparative pivotal trials. No unexpected adverse events were recorded. Most adverse events were attributed to anthracycline-based chemotherapy, with gastrointestinal and haematological toxicity as the most prominent characteristics, although due to the absence of a control group difficult to determine. Local examination should be performed on regular basis after treatment until resolution (see SPC, section 4.4).

Dexrazoxane has not been studied in patients with impaired renal or hepatic function and its use in such patients is not recommended (see SPC, section 4.2). Since liver dysfunction (increases in transaminases and bilirubin) may occur (especially after high doses above 1 g/m^2 dexrazoxane), it is recommended that routine liver function tests are performed before each administration of dexrazoxane in patients with known liver function disorders (see SPC, section 4.4.). 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 (see SPC, section 4.4).

Due to considerable haematological toxicity in one published phase 1 study [5] with doses lower than the proposed posology, regular haematological monitoring is recommended (see SPC, section 4.4.). Patients with neutropenia and thrombocytopenia > CTC grade 1 have not been included in the clinical studies (see SPC, section 4.4).

As the solution for infusion contains potassium (98mg/500ml) the plasma potassium level of the patient must be closely monitored in patients at risk of hyperkalaemia. It also contains sodium (1.61g/500ml) which may be harmful to patients on a low sodium diet (see SPC, section 4.4.).

Safety and MTD results from phase I antineoplastic studies showed that MTD was dependent on age, posology and dosing schedule and varied from 3500 mg/m² 2-hour i.v. infusion for 3 days to 7420 mg/m² when given once weekly, with myelosuppression and abnormal liver function tests becoming dose-limiting. The MTD was lower in patients who have been heavily pre-treated with chemotherapy and those with pre-existing immunosuppression. The given dose schedule is far below these MTDs and no modification is recommended (see SPC, section section 4.2). The treatment is not recommended to paediatric and elderly patients (see SPC, section 4.2).

Pharmacovigilance

Detailed description of the Pharmacovigilance system
The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan
The CHMP did not require the MAA to submit a risk management plan because the side effects of dexrazoxane are well-known due to 20 years of observation in other indications. For the new indication it is used as an antidote in an emergency situation with a fixed treatment schedule of 3 days.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology
Two pharmacodynamic properties of dexrazoxane, its antineoplastic effect and its use in the prevention of anthracycline cardiotoxicity, are well described in the literature.
Dexrazoxane has been shown to possess mutagenic activity. The carcinogenic potential of dexrazoxane has not been investigated, however, razoxane, (the racemic mixture of dexrazoxane and levrazoxane), has been reported to be associated with the development of secondary malignancies in mice (lymphoid neoplasms) and rats (uterine carcinomas) after administration for a prolonged period of time. Both of these effects are expected for this class of compound.

Repeat-dose toxicity studies have shown that primary target organs were tissues that undergo rapid cell division: bone marrow, lymphoid tissue, testes and digestive tract. Myelosuppression is thus common. The apparent effects were greater during chronic administration than acute. The toxicity in combination with doxorubicin was additive and not synergistic.

The related razoxane has been demonstrated to be embryotoxic in mice, rats and rabbits and teratogenic in rats and mice.

When mice with experimental daunorubicin extravasation were treated with dexrazoxane systemically combined with topical treatment with DMSO on the daunorubicin-affected skin area, 67% of the mice developed small skin wounds, whereas dexrazoxane treatment alone completely prevented the daunorubicin induced skin necrosis in another group of mice, Thus, DMSO should not be used in patients treated with dexrazoxane to prevent anthracycline extravasation.

Efficacy
The clinical programme for dexrazoxane included two open, single arm, multicentre studies.
The overall purpose of each trial was to investigate the efficacy of intravenous dexrazoxane in preventing tissue damage from accidentally extravasated anthracycline, and thus preventing the patients from undergoing the routinely used surgical excision of the affected tissue.

Treatment with dexrazoxane had to be started within 6 hours from the incident and was repeated after 24 and 48 hours. The first and second doses were at 1000 mg/m^2 and the third was 500 mg/m^2. A requirement for inclusion in the efficacy part of the study was that the anthracycline extravasation was proven by fluorescence microscopy of one or more biopsies.

In study TT01 23 patients were entered and received treatment with dexrazoxane. Eighteen were evaluable for efficacy and safety and a further five patients were evaluable for toxicity only. None of the patients required surgical intervention.

In study TT02, 57 patients entered the study and received the first dose of dexrazoxane. 36 patients were evaluable for efficacy. Only one of the 36 patients required surgery.
In both studies dexrazoxane treatment prevented the development of necrosis, allowed cancer treatment to continue as scheduled in the majority of patients, and reduced the occurrence of sequelae.

Safety
A number of published reports comprising more than 1000 patients have demonstrated a uniform pattern of dose dependant adverse reactions such as nausea/vomiting, diarrhoea, stomatitis, bone marrow suppression (neutropenia, thrombocytopenia) and affected liver function (increased ALT/AST). All adverse reactions have been rapidly reversible.

From the safety database, all the adverse reactions reported in clinical trials were included in the Summary of Product Characteristics. Based on two clinical studies, TT01 and TT02, conducted in patients with extravasation receiving dexrazoxane and already receiving cycles of chemotherapeutic agents, the adverse reactions reported were those typically seen with standard chemotherapy, i.e. nausea/vomiting in about a third, neutropenia and thrombocytopenia in about half, more rarely increased concentration of liver enzymes (ALT/AST).

Risk-benefit assessment
Anthracycline extravasation is a worrying and serious complication of cytotoxics administration that may lead to progressive tissue necrosis necessitating surgical resection. The condition is rare and the clinical profile is heterogeneous. Several methods are available to treat suspected anthracycline extravasation such as local cooling, Dimethylsulfoxide (DMSO), corticosteroids, and in some countries surgical resection of the affected tissue in patients with biopsy-verified (fluorescence-positive) anthracycline extravasation. No trial comparing available treatment principles was conducted. Currently there are no authorised products for the treatment of anthracycline extravasation.

The present application was for a new systemic antidote treatment, dexrazoxane. Dexrazoxane is a product that has been approved since 1992 for the prevention of cardiotoxicity in breast cancer treated by doxorubicin in several countries. The toxicity profile of the compound is well known and similar to that seen with topoisomerase inhibitors. There were two efficacy and safety studies in the application, study TT01 and TT02. Both studies were multicentre, open label, single arm. phase II (TT01) and phase II-III (TT02) studies. The demonstration of efficacy was based on comparison with results described in the literature. The number of patients studied was limited (80 patients in total). Both studies reached the primary objective. In TT01, none of the evaluable patients underwent surgery as a consequence of the extravasation. In TT02, the proportion was one out of 36 evaluable for efficacy patients. The effect of dexrazoxane was considered as clinically relevant in a condition where no standard treatment is authorised and where no clinical trial had been previously conducted.

However in clinical practice, biopsy could be not available in all centres, neither for all patients (e.g. central venous access device CVAD). In this situation the administration of dexrazoxane could be questionable as the efficacy data for dexrazoxane applied to patients in whom the biopsy was positive only. Considering that in both clinical trials, none of the patients excluded from the efficacy analyses due to a negative biopsy, required surgical intervention, it was considered that dexrazoxane could be indicated for patients in whom biopsy is not feasible.

At the time of the assessment, the safety profile of dexrazoxane was considered similar to the safety of the same product used for other authorised indication(including nausea/vomiting, diarrhoea, stomatitis, bone marrow suppression). No unexpected adverse events were recorded in the two non-comparative pivotal trials. Gastro-intestinal and administration site condition were the most reported class effects. Most adverse events could be attributed to anthracycline based chemotherapy, with gastrointestinal and haematological toxicity as the most prominent characteristics. There were some injection site reactions and infections at the biopsy sites were seen in several patients and it is possible that there was some contribution of dexrazoxane to the side effects otherwise typical of anthracycline-based chemotherapy, i.e. nausea, vomiting, and reversible haematological toxicity. When using the NCI-CTC system the frequency of Grade 3-4 toxicity seems relatively low, although laboratory neutropenia was recorded in a substantial number of cases.

The generally favourable safety profile was confirmed by the small number of patients discontinuing treatment due to adverse events. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

No major objections were identified during the Marketing Authorisation application. Satisfactory responses were given to the CHMP Lists of Questions.

Therefore the benefit/risk ratio of dexrazoxane for the treatment of anthracycline extravasation is considered positive and an approval of the application is recommended.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Savene is not similar to any of the currently authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Market exclusivity

Not applicable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Savene in the treatment of anthracycline extravasation was favourable and therefore recommended the granting of the marketing authorisation.

References

1. Herman EH, Ferrans VJ, Jordan W, Ardalan B: **Reduction of chronic daunorubicin cardiotoxicity by ICRF-187 in rabbits**. *Res Commun Chem Pathol Pharmacol* 1981, **31**(1):85-97.
2. Herman EH, Balazs T, Ferrans VJ, Young RS: **Divergent effects of propranolol and furosemide pretreatment on acute cardiomyopathy induced by minoxidil in beagle dogs**. *Toxicology* 1981, **20**(2-3):155-164.
3. Perkins WE, Schroeder RL, Carrano RA, Imondi AR: **Effect of ICRF-187 on doxorubicin-induced myocardial effects in the mouse and guinea pig**. *Br J Cancer* 1982, **46**(4):662-667.
4. Villani F, Galimberti M, Monti E, Cova D, Lanza E, Rozza-Dionigi A, Favalli L, Poggi P: **Effect of ICRF-187 pretreatment against doxorubicin-induced delayed cardiotoxicity in the rat**. *Toxicol Appl Pharmacol* 1990, **102**(2):292-299.
5. Della Torre P, Podesta A, Pinciroli G, Iatropoulos MJ, Mazue G: **Long-lasting effect of dexrazoxane against anthracycline cardiotoxicity in rats**. *Toxicol Pathol* 1996, **24**(4):398-402.
6. Poster DS, Penta JS, Bruno S, Macdonald JS: **ICRF-187 in clinical oncology**. *Cancer Clin Trials* 1981, **4**(2):143-146.
7. Wadler S, Green MD, Basch R, Muggia FM: **Lethal and sublethal effects of the combination of doxorubicin and the bisdioxopiperazine, (+)-1,2,-bis (3-5-dioxopiperazinyl-1-yl) propane (ICRF 187), on murine sarcoma S180 in vitro**. *Biochem Pharmacol* 1987, **36**(9):1495-1501.
8. von Hoff DD, Soares N, Gormley P, Poplack DG: **Pharmacokinetics of ICRF-187 in the cerebrospinal fluid of subhuman primates**. *Cancer Treat Rep* 1980, **64**(4-5):734-736.
9. Hasinoff BB: **The hydrolysis activation of the doxorubicin cardioprotective agent ICRF-187 [+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane)**. *Drug Metab Dispos* 1990, **18**(3):344-349.
10. Hasinoff BB: **Enzymatic ring-opening reactions of the chiral cardioprotective agent (+) (S)-ICRF-187 and its (-) (R)-enantiomer ICRF-186 by dihydropyrimidine amidohydrolase**. *Drug Metab Dispos* 1993, **21**(5):883-888.
11. Hasinoff BB, Aoyama RG: **Relative plasma levels of the cardioprotective drug dexrazoxane and its two active ring-opened metabolites in the rat**. *Drug Metab Dispos* 1999, **27**(2):265-268.
12. Baldwin JR, Lewis RC, Phillips BA, Overmyer SK, Hatfield NZ, Narang PK: **Dose-independent pharmacokinetics of the cardioprotective agent dexrazoxane in dogs**. *Biopharm Drug Dispos* 1996, **17**(6):541-550.
13. Vaidyanathan S, Boroujerdi M: **Interaction of dexrazoxane with red blood cells and hemoglobin alters pharmacokinetics of doxorubicin**. *Cancer Chemother Pharmacol* 2000, **46**(2):93-100.
14. Cusack BJ, Musser B, Gambliel H, Hadjokas NE, Olson RD: **Effect of dexrazoxane on doxorubicin pharmacokinetics in young and old rats**. *Cancer Chemother Pharmacol* 2003, **51**(2):139-146.
15. Baldwin JR, Phillips BA, Overmyer SK, Hatfield NZ, Narang PK: **Influence of the cardioprotective agent dexrazoxane on doxorubicin pharmacokinetics in the dog**. *Cancer Chemother Pharmacol* 1992, **30**(6):433-438.
16. Hofland KF, Thougaard AV, Dejligbjerg M, Jensen LH, Kristjansen PE, Rengtved P, Sehested M, Jensen PB: **Combining etoposide and dexrazoxane synergizes with radiotherapy and improves survival in mice with central nervous system tumors**. *Clin Cancer Res* 2005, **11**(18):6722-6729.
17. Pearlman M, Jendiroba D, Pagliaro L, Keyhani A, Liu B, Freireich EJ, Travis E: **Dexrazoxane's protection of jejunal crypt cells in the jejunum of C3Hf/Kam mice from doxorubicin-induced toxicity**. *Cancer Chemother Pharmacol* 2003, **52**(6):477-481.
18. Zima T, Tesar V, Sherwood R, Sood A, Au LC, Richardson PJ, Preedy VR: **Acute dosage with dexrazoxane, but not doxorubicin, is associated with increased rates of hepatic protein synthesis in vivo**. *Toxicol Pathol* 2001, **29**(6):591-599.

19. Herman EH, el-Hage A, Ferrans VJ: **Protective effect of ICRF-187 on doxorubicin-induced cardiac and renal toxicity in spontaneously hypertensive (SHR) and normotensive (WKY) rats**. *Toxicol Appl Pharmacol* 1988, **92**(1):42-53.
20. Dardir M, Herman EH, Ferrans VJ: **Effects of ICRF-187 on the cardiac and renal toxicity of epirubicin in spontaneously hypertensive rats**. *Cancer Chemother Pharmacol* 1989, **23**(5):269-275.
21. Zima T, Tesar V, Crkovska J, Stejskalova A, Platenik J, Teminova J, Nemecek K, Janebova M, Stipek S: **ICRF-187 (dexrazoxan) protects from adriamycin-induced nephrotic syndrome in rats**. *Nephrol Dial Transplant* 1998, **13**(8):1975-1979.
22. Zhang J, Clark JR, Jr., Herman EH, Ferrans VJ: **Doxorubicin-induced apoptosis in spontaneously hypertensive rats: differential effects in heart, kidney and intestine, and inhibition by ICRF-187**. *J Mol Cell Cardiol* 1996, **28**(9):1931-1943.
23. Herman EH, Ferrans VJ, Myers CE, Van Vleet JF: **Comparison of the effectiveness of (+/-)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane (ICRF-187) and N-acetylcysteine in preventing chronic doxorubicin cardiotoxicity in beagles**. *Cancer Res* 1985, **45**(1):276-281.
24. Herman EH, Ferrans VJ: **Timing of treatment with ICRF-187 and its effect on chronic doxorubicin cardiotoxicity**. *Cancer Chemother Pharmacol* 1993, **32**(6):445-449.
25. Herman EH, Ferrans VJ, Young RS, Hamlin RL: **Effect of pretreatment with ICRF-187 on the total cumulative dose of doxorubicin tolerated by beagle dogs**. *Cancer Res* 1988, **48**(23):6918-6925.
26. Herman EH, Ferrans VJ: **Reduction of chronic doxorubicin cardiotoxicity in dogs by pretreatment with (+/-)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane (ICRF-187)**. *Cancer Res* 1981, **41**(9 Pt 1):3436-3440.
27. Albanese R, Watkins PA: **The mutagenic activity of razoxane (ICRF 159): an anticancer agent**. *Br J Cancer* 1985, **52**(5):725-731.
28. Wang L, Eastmond DA: **Catalytic inhibitors of topoisomerase II are DNA-damaging agents: induction of chromosomal damage by merbarone and ICRF-187**. *Environ Mol Mutagen* 2002, **39**(4):348-356.
29. Wang G, Finch MD, Trevan D, Hellmann K: **Reduction of daunomycin toxicity by razoxane**. *Br J Cancer* 1981, **43**(6):871-877.
30. Herman EH, el-Hage AN, Creighton AM, Witiak DT, Ferrans VJ: **Comparison of the protective effect of ICRF-187 and structurally related analogues against acute daunorubicin toxicity in Syrian golden hamsters**. *Res Commun Chem Pathol Pharmacol* 1985, **48**(1):39-55.
31. Herman EH ZJ, Rifai N, Lipshultz SE, Hasinoff BB, Chadwick DP, Knapton A, Chai J, Ferrans VJ.: **The use of serum levels of cardiac troponin T to compare the protective activity of dexrazoxane against doxorubicin- and mitoxantrone-induced cardiotoxicity.** *Cancer Chemother Pharmacol* 2001, **48**(4):297-304.
32. Earhart RH, Tutsch KD, Koeller JM, Rodriguez R, Robins HI, Vogel CL, Davis HL, Tormey DC: **Pharmacokinetics of (+)-1,2-di(3,5-dioxopiperazin-1-yl)propane intravenous infusions in adult cancer patients**. *Cancer Res* 1982, **42**(12):5255-5261.
33. Holcenberg JS, Tutsch KD, Earhart RH, Ungerleider RS, Kamen BA, Pratt CB, Gribble TJ, Glaubiger DL: **Phase I study of ICRF-187 in pediatric cancer patients and comparison of its pharmacokinetics in children and adults**. *Cancer Treat Rep* 1986, **70**(6):703-709.
34. Vogel CL, Gorowski E, Davila E, Eisenberger M, Kosinski J, Agarwal RP, Savaraj N: **Phase I clinical trial and pharmacokinetics of weekly ICRF-187 (NSC 169780) infusion in patients with solid tumors**. *Invest New Drugs* 1987, **5**(2):187-198.
35. Tetef ML, Synold TW, Chow W, Leong L, Margolin K, Morgan R, Raschko J, Shibata S, Somlo G, Yen Y *et al*: **Phase I trial of 96-hour continuous infusion of dexrazoxane in patients with advanced malignancies**. *Clin Cancer Res* 2001, **7**(6):1569-1576.
36. Hochster H, Liebes L, Wadler S, Oratz R, Wernz JC, Meyers M, Green M, Blum RH, Speyer JL: **Pharmacokinetics of the cardioprotector ADR-529 (ICRF-187) in escalating doses combined with fixed-dose doxorubicin**. *J Natl Cancer Inst* 1992, **84**(22):1725-1730.
37. Rosing H, ten Bokkel Huinink WW, van Gijn R, Rombouts RF, Bult A, Beijnen JH: **Comparative open, randomized, cross-over bioequivalence study of two intravenous**

dexrazoxane formulations (Cardioxane and ICRF-187) in patients with advanced breast cancer, treated with 5-fluorouracil-doxorubicin-cyclophosphamide (FDC). *Eur J Drug Metab Pharmacokinet* 1999, **24**(1):69-77.
38. Jakobsen P, Sorensen B, Bastholt L, Mirza MR, Gjedde SB, Mouridsen HT, Rose C: **The pharmacokinetics of high-dose epirubicin and of the cardioprotector ADR-529 given together with cyclophosphamide, 5-fluorouracil, and tamoxifen in metastatic breast-cancer patients**. *Cancer Chemother Pharmacol* 1994, **35**(1):45-52.
39. Basser RL, Sobol MM, Duggan G, Cebon J, Rosenthal MA, Mihaly G, Green MD: **Comparative study of the pharmacokinetics and toxicity of high-dose epirubicin with or without dexrazoxane in patients with advanced malignancy**. *J Clin Oncol* 1994, **12**(8):1659-1666.
40. Schroeder PE, Jensen PB, Sehested M, Hofland KF, Langer SW, Hasinoff BB: **Metabolism of dexrazoxane (ICRF-187) used as a rescue agent in cancer patients treated with high-dose etoposide**. *Cancer Chemother Pharmacol* 2003, **52**(2):167-174.
41. Hasinoff BB: **Chemistry of dexrazoxane and analogues**. *Semin Oncol* 1998, **25**(4 Suppl 10):3-9.
42. Tanabe K, Ikegami Y, Ishida R, Andoh T: **Inhibition of topoisomerase II by antitumor agents bis(2,6-dioxopiperazine) derivatives**. *Cancer Res* 1991, **51**(18):4903-4908.
43. Von Hoff DD, Howser D, Lewis BJ, Holcenberg J, Weiss RB, Young RC: **Phase I study of ICRF-187 using a daily for 3 days schedule**. *Cancer Treat Rep* 1981, **65**(3-4):249-252.
44. Liesmann J, Belt R, Haas C, Hoogstraten B: **Phase I evaluation of ICRF-187 (NSC-169780) in patients with advanced malignancy**. *Cancer* 1981, **47**(8):1959-1962.
45. Koeller JM, Earhart RH, Davis HL: **Phase I trial of ICRF-187 by 48-hour continuous infusion**. *Cancer Treat Rep* 1981, **65**(5-6):459-463.
46. Vats T, Kamen B, Krischer JP: **Phase II trial of ICRF-187 in children with solid tumors and acute leukemia**. *Invest New Drugs* 1991, **9**(4):333-337.
47. Langer SW, Sehested M, Jensen PB, Buter J, Giaccone G: **Dexrazoxane in anthracycline extravasation**. *J Clin Oncol* 2000, **18**(16):3064.
48. Jensen JN, Lock-Andersen J, Langer SW, Mejer J: **Dexrazoxane-a promising antidote in the treatment of accidental extravasation of anthracyclines**. *Scand J Plast Reconstr Surg Hand Surg* 2003, **37**(3):174-175.
49. Bos AM, van der Graaf WT, Willemse PH: **A new conservative approach to extravasation of anthracyclines with dimethylsulfoxide and dexrazoxane**. *Acta Oncol* 2001, **40**(4):541-542.
50. El-Saghir N, Otrock Z, Mufarrij A, Abou-Mourad Y, Salem Z, Shamseddine A, Abbas J: **Dexrazoxane for anthracycline extravasation and GM-CSF for skin ulceration and wound healing**. *Lancet Oncol* 2004, **5**(5):320-321.