ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Savene 20 mg/ml powder and solvent for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg dexrazoxane (589 mg dexrazoxane hydrochloride).
Each ml contains 20 mg of dexrazoxane after reconstitution with 25 ml of Savene solvent.

Excipients with known effects:
Solvent bottle:
Potassium 98 mg/500 ml or 5.0 mmol/l
Sodium 1.61 g/500 ml or 140 mmol/l

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.

Powder vial:
White to off-white lyophilisate.

Solvent bottle:
Clear isotonic solution (295 mOsml/l, pH approx. 7.4).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Savene is indicated in adults for the treatment of anthracycline extravasation.

4.2 Posology and method of administration

Savene must be administered under the supervision of a physician experienced in the use of anti-cancer medicinal products.

Posology
Treatment should be given once daily for 3 consecutive days. The recommended dose is:
Day 1: 1000 mg/m^2
Day 2: 1000 mg/m^2
Day 3: 500 mg/m^2

The first infusion should be initiated as soon as possible, within the first six hours after the accident. Treatment Day 2 and Day 3 should start at the same hour (+/- 3 hours) as Day 1.

For patients with a body surface area of more than 2 m^2 the single dose should not exceed 2000 mg.

Renal impairment
In patients with moderate to severe renal impairment (creatinine clearance <40 mL/min) the Savene dose should be reduced by 50% (see section 4.4 and 5.2).

Hepatic impairment
Dexrazoxane has not been studied in patients with impaired hepatic function and its use in such patients is not recommended (see section 4.4).

Elderly
Safety and efficacy have not been evaluated in the elderly and the use of dexrazoxane in such patients is not recommended.

Paediatric population
The safety and efficacy of Savene in children below the age of 18 years have not been established and no data are available.

Method of administration
For intravenous use after reconstitution and dilution.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.
The indicated dose should be administered as an intravenous infusion over 1-2 hours into a large vein of an extremity or area other than the one affected by the extravasation. Cooling procedures such as ice packs should have been removed from the area at least 15 minutes before the Savene administration in order to allow sufficient blood flow.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women of childbearing potential not using contraceptive measures (see section 4.6).
- Breast-feeding (see section 4.6).
- Concomitant vaccination with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Continuous monitoring
Local examination should be performed on a regular basis after treatment until resolution.

If there is suspicion of extravasation by vesicant compounds other than anthracyclines through the same IV access, e.g. vincristine, mitomycin, and vinorelbine, Savene would not be effective against the effects from these compounds.

Since Savene will be administered to patients undergoing cytotoxic therapy with anthracyclines its cytotoxic potential (especially resulting in reversible haematological toxicity with a nadir occurring on days 11-12) will therefore add to that of the other chemotherapy administered. Haematological monitoring should therefore be undertaken regularly.

Hepatic and renal-function monitoring
Since liver dysfunction (increases in transaminases and bilirubin) may occur (especially after doses of above 1 000 mg/m^2 dexrazoxane), it is recommended that routine liver function tests be performed before each administration of dexrazoxane in patients with known liver function disorders (see section 4.2).

Since renal dysfunction may decrease the rate of elimination of dexrazoxane, patients with impaired renal function should be monitored for signs of haematological toxicity (see section 4.2 for dosing recommendations in patients with moderate to severe renal impairment (creatinine clearance <40 mL/min)).

Anaphylactic reaction
Anaphylactic reaction including angioedema, skin reactions, bronchospasm, respiratory distress, hypotension and loss of consciousness have been observed in patients treated with dexrazoxane and

anthracyclines (see section 4.8). Previous history of allergy to dexrazoxane should be carefully considered prior to administration (see section 4.3).

Women of child-bearing potential/Contraception in males and females
Since dexrazoxane possesses mutagenic activity and is used with anthracyclines known to have cytotoxic, mutagenic and embryotoxic properties, both sexually active men and women of childbearing potential should be advised not to father a child/become pregnant and must use effective contraceptive measures during and up to 6 months after treatment. Women must inform their doctor immediately if they become pregnant (see section 4.3 and 4.6).

Potassium and sodium contents
Savene solvent contains 98 mg potassium per 500 ml bottle. This must be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet. Plasma potassium level must be closely monitored in patients at risk of hyperkalaemia.
Savene solvent also contains 1.61 g sodium per 500 ml bottle, equivalent to 81% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated:
Yellow fever vaccine: Risk of fatal generalised vaccinial disease (see section 4.3).

Concomitant use not recommended:
- Other live attenuated vaccines: risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease or by concomitant chemotherapy. Use an inactivated vaccine where this exists (poliomyelitis).
- Dimethylsulfoxide (DMSO) should not be used in patients who are administered dexrazoxane to treat anthracycline extravasation (see section 5.3)
- Phenytoin: cytotoxic agents may reduce the absorption of phenytoin leading to an exacerbation of convulsions. Dexrazoxane is not recommended in combination with phenytoin.

Concomitant use to assess carefully:
Ciclosporin, tacrolimus: Excessive immunosuppression with risk of lymphoproliferative disease.

Interactions common to all cytotoxics:
- Due to an increased thrombotic risk in patients with malignant diseases, the use of anticoagulants treatment is frequent. Patients treated with anticoagulants should be monitored more frequently as cytotoxic agents may interact with oral anticoagulants.
- Dexrazoxane may add to the toxicity induced by the chemotherapy cycle during which the accident took place, requiring careful monitoring of haematological parameters (see section 4.4).

Interaction specific to dexrazoxane:
When tested in five major cytochrome P450 isoenzymes CYP1A, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, none of these were inhibited by dexrazoxane.

Co-administration of doxorubicin (50 to 60 mg/m^2) or epirubicin (60 to 100 mg/m^2) did not affect dexrazoxane pharmacokinetics significantly. In studies, dexrazoxane did not affect the pharmacokinetics of doxorubicin. There is limited evidence from studies that suggests epirubicin clearance may be increased when dexrazoxane is pre-administered, this occurred at high doses of epirubicin (120-135 mg/m^2). Note that in these studies dexrazoxane was administered prior to anthracyline administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Since dexrazoxane possesses mutagenic activity and is used with anthracyclines known to have cytotoxic, mutagenic and embryotoxic properties, both sexually active men and women of childbearing potential should be advised not to father a child/become pregnant and must use effective contraceptive measures during and up to 6 months after treatment. Women must inform their doctor immediately if they become pregnant (see section 4.3).

Pregnancy
There are no data from the use of dexrazoxane in pregnant women. Dexrazoxane may cause foetal harm when administered to pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Dexrazoxane should not be administered to pregnant women unless clearly necessary.

Breast-feeding
It is not known whether dexrazoxane is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants exposed to dexrazoxane, breast-feeding is contraindicated during Savene therapy (see section 4.3).

Fertility
There are limited fertility data from animal studies available, but testicular changes were observed in rats and rabbits following repeat dosing (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness, somnolence and syncope have been reported in a few patients included in Savene studies TT01 and TT02 (see section 4.8). Dexrazoxane has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

A number of published reports comprising more than 1000 patients have demonstrated a uniform pattern of dose dependent adverse reactions. Most common adverse reactions are nausea/vomiting, bone marrow suppression (neutropenia, thrombocytopenia), injection site reactions, diarrhoea, stomatitis and increase in hepatic transaminases (ALT/AST). All adverse reactions have been rapidly reversible.

The following information is based on two clinical studies, TT01 and TT02, of Savene administered to extravasation patients already receiving cycles of chemotherapeutic agents.

The adverse reactions were those typically seen with standard chemotherapy and also with dexrazoxane: Nausea/vomiting in about one third of the patients, neutropenia and thrombocytopenia in about half of the patients, more rarely increased concentration of liver enzymes (ALT/AST). Adverse reactions observed in the two studies are listed below.

Incidence of adverse reactions (MedDRA) in studies TT01 and TT02 (n=80 patients)
(Note that numbers for Blood and Lymphatic System Disorders are described in a separate table of laboratory examinations)
Adverse reactions reported are listed according to the following frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

System Organ Classes (SOC)	Frequency	Adverse reactions
Infections and infestations	Very common	Postoperative infection
	Common	Infection
		Neutropenic infection
Immune system disorders	Not known	Anaphylactic reactions
	Not known	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Common	Dizziness
		Sensory loss
		Syncope
		Tremor
Vascular disorders	Common	Phlebitis
		Superficial thrombophlebitis
		Venous thrombosis limb
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
		Pneumonia
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
		Diarrhoea
		Stomatitis
		Dry mouth
Skin and subcutaneous tissue disorders	Common	Alopecia
		Pruritus
Musculoskeletal and connective tissue disorders	Common	Myalgia
Reproductive system and breast disorders	Common	Vaginal haemorrhage
General disorders and administration site conditions	Very common	Injection site pain
	Common	Pyrexia
		Injection site phlebitis
		Injection site erythema
		Fatigue
		Injection site induration
		Injection site swelling
		Peripheral oedema
		Somnolence
Investigations	Common	Weight decreased
Injury, poisoning and procedural complications	Common	Wound complication

Incidence of laboratory abnormalities in TT01 and TT02 (n=80 patients)

Lab test	No of patients with post baseline value	CTC grade 3-4	
		N	%
Haemoglobin	80	2	2.5%
WBC	80	36	45.0%
Neutrophils	78	36	46.2%
Platelets	80	17	21.3%
Sodium (Hypo)	79	5	6.3%
Potassium (Hypo)	79	2	2.5%
Potassium (Hyper)	79	0	0.0%
Alkaline Phosphatase	77	0	0.0%
Bilirubin	77	1	1.3%
AST	57	2	3.5%
ALT	71	3	3.9%
Creatinine	76	2	2.6%
LDH	78	0	0.0%
Calcium Total (Hypo)	28	2	7.1%

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms of overdosage are likely to consist of leucopenia, thrombocytopenia, nausea, vomiting, diarrhoea, skin reactions and alopecia. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic agents, ATC code: V03AF02

Two pharmacodynamic properties of dexrazoxane are described in the literature:
1. Prevention of anthracycline cardiotoxicity, and
2. Antineoplastic action

Mechanism of action
Dexrazoxane has two major mechanisms of action:
1. Chelation of iron, especially through its ring-opened metabolite thus reducing the iron-dependent oxidative stress causing anthracycline-induced cardiotoxicity.
2. Inhibition of topoisomerase II.

It is not known to what extent each of these mechanisms contributes to the preventive effect on tissue destruction following anthracycline extravasation.

The chelating property is probably also responsible for an increased urinary excretion of iron and zinc and a decreased serum concentration of calcium as described in a few studies.

Clinical efficacy and safety
The clinical programme for Savene (dexrazoxane) included two open, single-arm, multicentre studies.

The overall purpose of each trial was to investigate the efficacy of intravenous Savene in preventing tissue damage from accidentally extravasated anthracycline, and thus preventing the patients from undergoing the routinely used surgical excision of the affected tissue.

Due to the rarity of the condition only historical data could be used for comparison (demonstrating surgical rates of 35-50 %, in one country 100% in biopsy proven cases).

In both studies the dosage regimen was the same. Treatment with Savene had to be started within 6 hours from the incident and was repeated after 24 and 48 hours. The first and second doses were 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.

For study purposes, patients with extravasations from a central venous access device (CVAD) were not included in the efficacy evaluation.

Patients with neutropenia and thrombocytopenia > CTC grade 1 (Common Toxicity Criteria) have not been included in the clinical studies.

In study **TT01**, 23 patients were entered and received treatment with Savene. 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 Savene. 36 patients were evaluable for efficacy. Only one of the 36 patients required surgery.

In both studies all patients had received anthracycline. Overall, the most commonly received anthracycline was epirubicin (56 % of the patients).

In both studies dexrazoxane treatment prevented the development of necrosis, allowed cancer treatment to continue as scheduled in the majority of patients (70.4 %), and reduced the occurrence of sequelae (only few and mild long-term sequelae were observed).

5.2 Pharmacokinetic properties

Savene must only be administered intravenously.

Distribution
Bibliographical data demonstrate that serum kinetics of dexrazoxane after intravenous administration follow an open two-compartment model independent of schedule and dose. The apparent volumes of distribution are 0.13-1.3 l/kg (median 0.49 l/kg). Volume of distribution is independent of dose. AUCs were dose-proportional. Tissue distribution is rapid, with the highest levels of unchanged parent compound and hydrolysed product appearing in liver and kidneys. About 2% of dexrazoxane is protein-bound.

Biotransformation
Dexrazoxane undergoes intracellular hydrolysis first to its two one-ring open intermediates (B and C) and then to the two-ring opened form (ADR-925) which has a structure similar to EDTA and is a strong chelator of iron and divalent cations as calcium ions.

Elimination
Dexrazoxane displays biphasic elimination kinetics. Initial elimination half lives (alpha) are 0.18-1 h (median 0.34 h) and terminal elimination half lives 1.9-9.1 h (median 2.8 h). Total urinary recovery of unchanged dexrazoxane is 34-60 %. Systemic clearance is independent of dose. The pharmacokinetics of the metabolites is derived from a single study with five patients. The mean elimination half-lives of the one-ring opened metabolite B and metabolite C are 0.9-3.9 h (n=5) and 0.5-0.8 h (n=3),

respectively. The elimination half-life of the two-ring opened metabolite ADR-925 is not given in literature. ADR-925 is reported to increase three-fold within 15 min after infusion of 1500 mg/m^2 and remain relatively constant on a plateau for 4 hours and then decreased to about half at 24 hours.

In-vitro studies on dexrazoxane in human microsomes have shown high stability of dexrazoxane indicating that major metabolism via cytochrome P450 is unlikely.

There is insufficient data available to draw any definite conclusions regarding 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.

Renal impairment
Compared with normal subjects (creatinine clearance (CLCR) >80 mL/min), exposure was 2- fold greater in subjects with moderate (CLCR of 30 to 50 mL/min) to severe (CLCR <30 mL/min) renal impairment. Modelling suggested that equivalent exposure ($AUC_{0\text{-}inf}$) could be achieved if dosing were reduced by 50% in subjects with CLCR less than 40 mL/min compared with control subjects (CLCR >80 mL/min) (see section 4.2).

Pharmacokinetics in patients with extravasations
Clinical trial TT04 was conducted on 6 female patients undergoing treatment for anthracycline extravasations. The aim was to examine the pharmacokinetics of a 3-day dosing regimen of dexrazoxane and its efficacy in patients for anthracycline extravasation. The systemic clearances were similar between day 1 (9.9 L/h ± 3.1) and day 2 (11.1 L/h ± 4.5), and did not differ from those reported in the literature. The steady-state volume of distribution of dexrazoxane was 30.5 L ± 11.1 for day 1 and 35.8 L ± 19.7 for day 2. The terminal elimination half-life was consistent throughout days 1 - 3 (2.1 - 2.2 h). The mean $AUC_{0\text{-}24}$ values for day 1 and day 2 were comparable with each other, and the $AUC_{0\text{-}last}$ at day 3 was approximately half that of the first two days, suggesting that the pharmacokinetics of dexrazoxane are dose-dependent. The overall ranges and mean of $AUC_{0\text{-}24}$ between days were very similar; it does not appear that there is any significant accumulation of dexrazoxane.

5.3 Preclinical safety data

Repeat-dose toxicity studies with dexrazoxane 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 than acute administration. The toxicity in combination with doxorubicin was additive and not synergistic. 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 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.

There are limited fertility data from animal studies available, but testicular changes were observed in rats and rabbits following repeat dosing.

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, dimethylsulfoxide (DMSO) should not be used in patients who are administered dexrazoxane to treat anthracycline extravasation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder vial
none

Solvent bottle
Sodium chloride
Potassium chloride
Magnesium chloride hexahydrate
Sodium acetate trihydrate
Sodium gluconate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Powder and solvent:
3 years.

After reconstitution and dilution:
Chemical and physical in-use stability has been demonstrated for 4 hours when stored at 2 to 8 °C.
From a microbiological point of view the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours at 2 to 8 °C.

6.4 Special precautions for storage

Store below 25 °C.
Keep the vials and bottles in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Savene powder:
Amber-coloured, 36-ml, glass type I vial with stopper made of chlorobutyl rubber and a flip-off cap.

Savene solvent:
500 ml solution in bottles made of Type-I (Ph.Eur.) glass.

Pack sizes:
Savene is available as an emergency kit consisting of 10 vials of Savene powder and 3 bottles of Savene solvent supplied with 3 bottle hangers.

6.6 Special precautions for disposal and other handling

Before infusion, Savene powder must be reconstituted with 25 ml Savene solvent to give a concentration of 20 mg dexrazoxane per ml. The concentrate is slightly yellow. The concentrate should then be diluted further in the remaining Savene solvent.

Caution must be exercised during reconstitution and dilution and the normal procedures for proper handling of cytotoxic medicinal products should be adopted. The preparation should not be handled by pregnant staff. Use of gloves and other protective clothing to prevent skin contact is recommended. Skin reactions have been reported following contact with dexrazoxane. If the powder or solution contacts the skin or mucous membranes, wash immediately and thoroughly with water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
1118BJ Schiphol
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/350/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 July 2006
Date of latest renewal: 18 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Cenexi-Laboratoires Thissen SA
Rue de la Papyrée 2-4-6
B-1420 Braine-L'Alleud
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

KIT BOX (1 KIT CONSISTING OF 10 POWDER VIALS AND 3 SOLVENT BOTTLES)

1. NAME OF THE MEDICINAL PRODUCT

Savene 20 mg/ml powder and solvent for concentrate for solution for infusion
dexrazoxane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg dexrazoxane (589 mg dexrazoxane hydrochloride).
After reconstitution with 25 ml Savene solvent, 1 ml of concentrate contains 20 mg dexrazoxane.

3. LIST OF EXCIPIENTS

Excipients Savene powder:
None
Excipients Savene solvent:
Sodium chloride
Potassium chloride
Magnesium chloride hexahydrate
Sodium acetate trihydrate
Sodium gluconate
Sodium hydroxide
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for concentrate for solution for infusion
10 vials of 500 mg dexrazoxane
3 bottles of 500 ml solvent and 3 bottle hangers

Emergency kit for the treatment of anthracycline extravasation

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be administered under the supervision of a physician experienced in the use of cytotoxic agents.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Concentrate and diluted solution may be stored at 2 to 8 °C for 4 hours.
Keep vials and bottles in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Contains cytotoxics.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
1118BJ Schiphol
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/350/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

< PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Savene 20 mg/ml powder for concentrate
dexrazoxane
Intravenous use after reconstitution and dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg dexrazoxane

6. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SOLVENT BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Savene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

Sodium chloride,
Potassium chloride,
Magnesium chloride hexahydrate,
Sodium acetate trihydrate,
Sodium gluconate,
Sodium hydroxide,
Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

500 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution with concentrate.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains cytotoxics after dilution with concentrate.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Keep in the outer carton in order to protect from light.
To be used within 4 hours after dilution when stored at 2-8 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/350/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

<Not applicable.>

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Savene 20 mg/ml powder and solvent for concentrate for solution for infusion
Dexrazoxane

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What Savene is and what it is used for

Savene contains the active substance dexrazoxane, which acts as an antidote to anti-cancer medicines called anthracyclines.

Most anti-cancer medicines are administered intravenously (into a vein). Occasionally an accident occurs and the medicine is infused outside the vein and into the surrounding tissue or leaks from the vein into the surrounding tissue. This event is called extravasation. It is a serious complication as it can cause severe tissue damage.

Savene is used to treat anthracyline extravasation in adults. It can reduce the amount of tissue damage caused by anthracycline extravasation.

2. What you need to know before you use Savene

Do not use Savene:
- If you are allergic to dexrazoxane or any of the other ingredients of this medicine (listed in section 6)
- If you are planning to become pregnant and do not use adequate contraceptive measures
- If you are breast-feeding
- If you are given yellow-fever vaccine

Warnings and precautions
Talk to your doctor or nurse before using Savene:
- Savene should only be given to you if you have an extravasation in connection with anthracycline-containing chemotherapy.
- During treatment with Savene the area where the extravasation has occurred will be examined on a regular basis and you will have blood tests taken regularly to check your blood cells.
- If you have liver problems, your doctor will monitor your liver function during treatment.
- If you have kidney problems, your doctor will monitor for signs of changes to your blood cells.

Children and adolescents
Savene should not be administered to children below the age of 18 years.

Other medicines and Savene
Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines.

In particular, tell your doctor or nurse if you are taking or may take any of the following medicines:
- Vaccines: you must not use Savene if you are going to receive yellow fever vaccine and it is not recommended that you use Savene if you are going to receive a vaccine containing live virus particles.
- A product called DMSO (which is a cream to treat some skin diseases).
- Phenytoin (a treatment against seizures) (Savene may reduce the effectiveness of this medicine).
- Anticoagulants (blood thinners) (your blood may need to be monitored more frequently).
- Ciclosporin or tacrolimus (both treatments lower the body's immune system and are used to prevent organ rejection after an organ transplant).
- Myelosuppressive medicines (decrease production of red, white, or coagulating blood cells).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby ask your doctor for advice before taking this medicine.
Savene should not be administered if you are pregnant.
You must not breast-feed while you are treated with Savene.
If you are sexually active, you are advised to use effective birth control to prevent pregnancy during and for six months after treatment, whether you are male or female (see section 2 'Do not use Savene').
There is limited information about the effect of Savene on fertility – if you have a concern about this speak to you doctor.

Driving and using machines
Dizziness, tiredness and sudden fainting have been reported in a few patients treated with Savene. The treatment is considered to have a limited influence on the ability to drive and use machines.

Savene contains potassium and sodium
The Savene solvent contains 98 mg potassium in each 500 ml bottle which may be harmful to people on a low-potassium diet or who have kidney problems. If you are at risk of high potassium levels in your blood, your doctor will monitor this.
Savene solvent also contains 1.61 g sodium (main component of cooking/table salt) in each 500 ml bottle. This is equivalent to 81% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Savene

Savene will be given to you under the control of a doctor experienced in the use of anti-cancer treatments.

Recommended dose
The dose will depend on your height, weight and kidney function. Your doctor will calculate your body surface area in square meter (m^2) to determine the dose you should receive. The recommended adult dose (with normal kidney function) is:

Day 1: 1000 mg/m^2
Day 2: 1000 mg/m^2
Day 3: 500 mg/m^2

Your doctor may reduce your dose if you have kidney problems.
Savene will be given by infusion into one of your veins. The infusion will last 1-2 hours.

Frequency of administration
You will receive your infusion once daily for 3 consecutive days. The first infusion will be given as soon as possible and within the first six hours after extravasation of an anthracycline medicine. Savene infusion will be given at the same time every day of your treatment.
Savene will not be used again at the time of your next anthracycline cycle, except if extravasation occurs again.

If you receive more Savene than you should
If you receive more Savene than you should, you will be closely monitored with specific attention to your blood cells, potential gastro-intestinal signs, skin reactions and hair loss.

If Savene comes into contact with the skin, the affected area should immediately be rinsed thoroughly with water.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention.
The following serious side effect has been reported in patients during treatment with Savene (frequency not known):
- Allergic reactions, symptoms of which could be itching (pruritis), rash, facial/throat swelling, wheezing, breathlessness or difficult breathing, changes in levels of consciousness, hypotension, sudden fainting

If you get any of the above symptoms, seek medical advice immediately.

Other possible side effects are listed below:

Very common: may affect more than 1 in 10 people
- Nausea
- Reactions at the site of injection (pain at the site, red, swollen or painful skin at the site or hardening of the skin at the site)
- Reduction in the number of white blood cells and platelets
- Infection (after an operation or other infections)

Common: may affect up to 1 in 10 people
- Vomiting
- Diarrhoea
- Feeling tired, feeling sleepy, feeling dizzy, sudden fainting
- Reduction in any of your senses (sight, smell, hearing, touch, taste)
- Fever
- Inflammation of the blood vessel where the treatment is given (phlebitis)
- Inflammation of a blood vessel just under the skin, often with a small blood clot
- Blood clot in the vein, usually in an arm or leg
- Inflammation in the mouth
- Dry mouth
- Hair loss
- Itching (pruritus)
- Weight loss, loss of appetite
- Muscle pain, tremor (uncontrolled muscle movement)
- Vaginal bleeding
- Difficulties in breathing

- Pneumonia (lung infection)
- Swelling in arms or legs (oedema)
- Wound complications
- Changes in liver function (these may be seen in test results)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Savene

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, powder vial label, and solvent bottle label after 'EXP'. The expiry date refers to the last day of that month.

Store below 25 °C.
Keep the powder vials and solvent bottles in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Savene contains
- The active substance is dexrazoxane. Each vial contains 500 mg dexrazoxane as 589 mg dexrazoxane hydrochloride.
- The other ingredient(s) are: The solvent which contains sodium chloride, potassium chloride, magnesium chloride hexahydrate, sodium acetate trihydrate, sodium gluconate, sodium hydroxide and water for injections.

What Savene looks like and contents of the emergency kit
The Savene kit consists of Savene powder for concentrate (white to off-white powder) and Savene solvent. One emergency kit contains 10 vials of Savene powder and 3 bottles of Savene solvent supplied with 3 bottle hangers.

The concentration of dexrazoxane following reconstitution with 25 ml Savene solvent is 20 mg/ml. The concentrate is slightly yellow.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
1118BJ Schiphol
The Netherlands

Manufacturer
Cenexi-Laboratoires Thissen SA
Rue de la Papyrée 2-4-6
B-1420 Braine-L'Alleud
Belgium

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only.

Preparation guide for use with Savene 20 mg/ml powder and solvent for concentrate for solution for infusion

It is important that you read the entire content of this procedure prior to the preparation of Savene.

1. FORMULATION

Savene is supplied as:
1. Savene powder for concentrate
2. Solvent for Savene

Savene powder must be reconstituted in 25 ml Savene solvent to obtain a concentrate that must be further diluted in the remaining Savene solvent prior to administration.

2. RECOMMENDATION FOR THE SAFE HANDLING

Savene is an anti-cancer agent and the normal procedures for proper handling and disposal of anti-cancer medicines should be adopted, namely:
- Personnel should be trained to reconstitute the medicine
- Pregnant staff should be excluded from working with this medicine
- Personnel handling this medicine during reconstitution should wear protective clothing including mask, goggles and gloves
- Accidental contact with the skin or eyes should be treated immediately and thoroughly with copious amounts of water

3. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

3.1 Reconstitution of Savene powder to prepare a concentrate

3.1.1 Using a syringe fitted with a needle, withdraw aseptically 25 ml from the Savene solvent bottle.
3.1.2 Inject the entire contents of the syringe into the vial containing the Savene powder.
3.1.3 Remove the syringe and needle and mix manually by repeated inversions until the powder is fully dissolved. Do not shake.
3.1.4 Allow the vial with the concentrate to stand for 5 minutes at room temperature and check if the solution is homogenous and clear. The concentrate is slightly yellow.
The concentrate contains 20 mg dexrazoxane per ml and should be used immediately for further dilution. It contains no antibacterial preservative.
3.1.5 Keep and store the opened solvent bottle under aseptic conditions because it is needed for dilution of the concentrate.

3.2 Dilution of the concentrate

3.2.1 Up to four vials containing Savene concentrate may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, withdraw aseptically the corresponding volume containing 20 mg dexrazoxane per ml from the appropriate number of vials containing concentrate. Use a graduated syringe filled with a needle.
3.2.2 Inject the required volume back into the opened Savene solvent bottle (see point 3.1.5). The solution must not be mixed with any other medicines.

3.2.3 Mix the solution by agitating gently the infusion bottle.
3.2.4 Savene should be administered aseptically as a 1-2 hours infusion under room temperature and normal light conditions.
3.2.5 As with all parenteral products, Savene concentrate and infusion solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions containing a precipitate should be discarded.

4. STORAGE

4.1 Before reconstitution and dilution:

- Store below 25 °C.
- Keep the powder vials and solvent bottles in the outer carton in order to protect from light.

4.2 After reconstitution and dilution:

- Chemical and physical in-use stability after reconstitution and subsequent dilution in the solvent has been demonstrated for 4 hours when stored at 2 to 8 °C.
- In order to avoid the potential contamination of the medicine by microbes, the product should be used immediately.
- If the medicine is not used immediately, it should be kept at a temperature of 2 to 8 °C (in the refrigerator) and no longer than 4 hours.

5. DISPOSAL

All items for preparation, administration or cleaning, including gloves, as well as liquid waste should be disposed of in accordance with local requirements.