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 1000 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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 pharmaco-kinetic 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_{0-24} values for day 1 and day 2 were comparable with each other, and the AUC_{0-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_{0-24} 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

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

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

01/10/2024