ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexrazoxane-containing medicinal products (See Annex I) 500 mg powder for solution for infusion.

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic adult breast cancer patients who have received a prior cumulative dose of 300 mg/m^2 of doxorubicin or a prior cumulative dose of 540 mg/m^2 of epirubicin when further anthracycline treatment is required.

4.2 Posology and method of administration

Posology
{(Invented) Name} is administered by a short intravenous infusion (15 minutes), approximately 30 minutes prior to anthracycline administration at a dose equal to 10 times the doxorubicin-equivalent dose and 10 times the epirubicin-equivalent dose.

Thus it is recommended that {(Invented) Name} is given at a dose of 500 mg/m^2 when the commonly used dosage schedule for doxorubicin of 50 mg/m^2 is employed or 600 mg/m^2 when the commonly used dosage schedule for epirubicin of 60 mg/m^2 is employed.

Paediatric population
{(Invented) Name} is contraindicated in children and adolescents up to 18 years of age (see section 4.3).

Renal impairment
In patients with moderate to severe renal dysfunction (creatinine clearance < 40 ml/min) the dexrazoxane dose should be reduced by 50%.

Hepatic impairment
The dosage ratio should be kept, i.e. if the anthracycline dose is reduced the dexrazoxane dose should be reduced accordingly.

Method of administration
Intravenous use.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Children and adolescents up to 18 years of age (see sections 4.4 and 4.8)
- Patients who are hypersensitive to dexrazoxane
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Myelosuppressive effects that may be additive to those of chemotherapy were reported with {(Invented) Name} (see section 4.8). Cell counts at nadir may be lower in patients treated with dexrazoxane. Haematological monitoring is thus necessary. Leucopenia and thrombocytopenia generally reverse quickly upon cessation of treatment with {(Invented) Name}.

At higher doses of chemotherapy, where the {(Invented) Name} dose exceeds 1000 mg/m^2, myelosuppression may increase significantly.

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

In clinical trials, second primary malignancies, in particular acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), have been reported in paediatric patients with Hodgkin's disease and acute lymphoblastic leukaemia receiving chemotherapy regimes including several cytotoxics (e.g. etoposide, doxorubicin, cyclophosphamide) (see section 4.8).

AML has been reported uncommonly in adult breast cancer patients post-marketing (see section 4.8).

In some studies, a higher incidence of death has been observed in the groups treated with dexrazoxane plus chemotherapy compared to those treated with chemotherapy alone. The possibility that dexrazoxane was a contributing factor to the imbalance cannot be ruled out (see section 5.1).

A significant decrease in tumour response rate has been reported in one study in advanced breast cancer patients treated with doxorubicin and dexrazoxane compared to patients treated with doxorubicin and placebo. Since both dexrazoxane and doxorubicin are topoisomerase inhibitors, it is possible that dexrazoxane may interfere with the anti-tumour efficacy of doxorubicin. Use of dexrazoxane in combination with adjuvant breast cancer therapy or chemotherapy intended as curative is therefore not recommended.

Clearance of dexrazoxane and its active metabolites may be reduced in patients with decreased creatinine clearance.

Liver dysfunction was occasionally observed in patients treated with {(Invented) Name} (see section 4.8).

Standard cardiac monitoring associated with doxorubicin or epirubicin treatment should be continued.

There are no data that support the use of dexrazoxane in patients with myocardial infarction within the past 12 months, pre-existing heart failure (including clinical heart failure secondary to anthracycline treatment), uncontrolled angina or symptomatic valvular heart disease.

Combination of dexrazoxane with chemotherapy may lead to an increased risk of thromboembolism (see section 4.8).

Since dexrazoxane is a cytotoxic agent, sexually active men should continue using effective methods of contraception for at least 3 months after cessation of treatment with dexrazoxane (see section 4.6).

Anaphylactic reaction including angioedema, skin reactions, bronchospasm, respiratory distress, hypotension and loss of consciousness have been observed in patients treated with {(Invented) Name}

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

4.5 Interaction with other medicinal products and other forms of interaction

{(Invented) Name} may increase haematological toxicity induced by chemotherapy or radiation, requiring careful monitoring of haematological parameters during the first two treatment cycles (see section 4.4).

Interaction studies with dexrazoxane are limited. Effects on CYP450 enzymes or drug transporters have not been studied.

{(Invented) Name} should not be mixed with any other medicinal products during infusion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Both sexually active men and women should use effective methods of contraception during treatment. For men the contraception should be continued for at least 3 months after cessation of treatment with {(Invented) Name} (see section 4.4).

Pregnancy
There are no adequate data from the use of dexrazoxane in pregnant women. Animal studies showed embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. {(Invented) Name} should not be used during pregnancy unless clearly necessary.

Breast-feeding
There are no animal studies on the transfer of the active substance and/or its metabolites into milk. It is unknown whether dexrazoxane and/or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in infants exposed to {(Invented) Name}, mothers should discontinue breast-feeding during {(Invented) Name} therapy (see section 4.3).

Fertility
The effects of {(Invented) Name} on the fertility of humans and animals have not been studied.

4.7 Effects on ability to drive and use machines

Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with {(Invented) Name}.

4.8 Undesirable effects

{(Invented) Name} is administered together with anthracycline chemotherapy and, consequently, the relative contributions of anthracycline and {(Invented) Name} to the adverse reaction profile may be unclear. The most common adverse reactions are haematological and gastroenterological reactions, primarily anaemia, leukopenia, nausea, vomiting and stomatitis, as well as asthenia and alopecia. Myelosuppressive effects of {(Invented) Name} may be additive to those of chemotherapy (see section 4.4). An increased risk of the development of second primary malignancies, particularly AML, has been reported.

Adverse reactions
The following table includes reactions from clinical trials and from post-marketing use. Due to the spontaneous nature of post-marketing reporting, such events are listed with frequency “not known” if they were not already identified as reactions from clinical trials.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); not known (cannot be estimated from the available data).

Table 1

Infections and infestations	
Uncommon	Infection, sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Acute myeloid leukaemia
Blood and lymphatic system disorders	
Very common	Anaemia, leukopenia
Common	Neutropenia, thrombocytopenia, febrile neutropenia, granulocytopenia
Uncommon	Febrile bone marrow aplasia, eosinophil count increased, neutrophil count increased, platelet count increased, white blood cell count increased, lymphocyte count decreased, monocyte count decreased
Immune system disorders	
Not known	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	
Common	Anorexia
Nervous system disorders	
Common	Paraesthesia, dizziness, headache, peripheral neuropathy
Uncommon	Syncope
Eye disorders	
Common	Conjunctivitis
Ear and labyrinth disorders	
Uncommon	Vertigo, ear infection
Cardiac disorders	
Common	Ejection fraction decreased, tachycardia
Vascular disorders	
Common	Phlebitis
Uncommon	Venous thrombosis, lymphoedema
Not known	Embolism
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough, pharyngitis
Uncommon	Respiratory tract infection
Not known	Pulmonary embolism
Gastrointestinal disorders	
Very common	Nausea, vomiting, stomatitis
Common	Diarrhoea, constipation, abdominal pain, dyspepsia
Uncommon	Gingivitis, oral candidiasis
Hepatobiliary disorders	
Common	Transaminases increased
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Nail disorder, erythema
General disorders and administration site conditions	
Very common	Asthenia
Common	Mucosal inflammation, pyrexia, fatigue, malaise, injection site reaction (including pain, swelling, burning sensation, erythema, pruritus, thrombosis)
Uncommon	Oedema, thirst

Clinical trial data

The above table shows adverse reactions reported in clinical studies and having a reasonable possibility of a causal relationship with {(Invented) Name}. These data are derived from clinical trials in cancer patients where {(Invented) Name} was used in combination with anthracycline-based

chemotherapy, and where in some cases a control group of patients receiving chemotherapy alone can be referred to.

Patients receiving chemotherapy and {(Invented) Name} (n=375):

- Of these 76% were treated for breast cancer and 24% for a variety of advanced cancers.
- {(Invented) Name} treatment: a mean dose of 1010 mg/m² (median: 1000 mg/m²) in combination with doxorubicin, and a mean dose of 941 mg/m² (median: 997 mg/m²) in combination with epirubicin.
- Chemotherapy treatment received by patients treated for breast cancer: 45% combination therapy with doxorubicin 50 mg/m² (mainly with 5-fluorouracil and cyclophosphamide): 17% with epirubicin alone; 14% combination therapy with epirubicin 60 or 90 mg/m² (mainly with 5-fluorouracil and cyclophosphamide).

Patients receiving chemotherapy alone (n=157)

- All were treated for breast cancer
- Chemotherapy treatment received: 43% single agent epirubicin 120 mg/m²; 33% combination therapy with 50 mg/m² doxorubicin (mainly with 5-fluorouracil and cyclophosphamide); 24% combination therapy with epirubicin at 60 or 90 mg/m² (mainly with 5-fluorouracil and cyclophosphamide).

Second primary malignancies

Secondary acute myeloid leukaemia (AML) / myelodysplastic syndrome (MDS) has been observed in paediatric patients with Hodgkin's disease or acute lymphoblastic leukaemia receiving dexrazoxane in combination with chemotherapy (see section 4.4). AML has been reported uncommonly in adult breast cancer patients post-marketing.

Safety profile at maximum tolerated dose

Dexrazoxane's maximum tolerated dose (MTD) when given as monotherapy by short infusion every three weeks for cardioprotection has not been specifically studied. In studies of dexrazoxane as a cytotoxic, its MTD is shown to be dependent on posology and dosing schedule, and varies from 3750 mg/m^2 when short infusions are given in divided doses over 3 days to 7420 mg/m^2 when given weekly for 4 weeks, with myelosuppression and abnormal liver function tests becoming dose-limiting. The MTD is lower in patients who have been heavily pre-treated with chemotherapy, and those with pre-existing immunosuppression (e.g. AIDS).

The following are adverse reactions reported when {(Invented) Name} was given at doses around the MTD: neutropenia, thrombocytopenia, nausea, vomiting, and increase in hepatic parameters. Other toxic effects were malaise, low grade fever, increased urinary clearance of iron and zinc, anaemia, abnormal blood clotting, transient elevation of serum triglyceride and amylase levels, and a transient decrease in serum calcium level.

4.9 Overdose

The signs and symptoms of overdose are likely to consist of leucopenia, thrombocytopenia, nausea, vomiting, diarrhoea, skin reactions and alopecia. There is no specific antidote and symptomatic treatment should be provided.

Management should include prophylaxis and treatment of infections, fluid regulation, and maintenance of nutrition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The exact mechanism by which dexrazoxane exerts its cardioprotective effect has not been fully elucidated, however based on the available evidence the following mechanism has been suggested. The dose-dependent cardiotoxicity observed during anthracycline administration is due to anthracycline-induced iron-dependent free radical oxidative stress on the relatively unprotected cardiac muscle. Dexrazoxane, an analogue of EDTA (ethylene diamine tetra-acetic acid), is hydrolysed in cardiac cells to the ring-opened product ICRF-198. Both dexrazoxane (ICRF-187) and ICRF-198 are capable of chelating metal ions. It is generally thought that they can provide cardioprotection by scavenging metal ions thus preventing the Fe3+-anthracycline complex from redox cycling and forming reactive radicals.

The evidence from clinical trials to date suggests increasing cardioprotective benefit from dexrazoxane as the cumulative anthracycline dose is increased.

Dexrazoxane does not protect against non-cardiac toxicities induced by anthracyclines.

The majority of controlled clinical studies were performed in patients with advanced breast cancer. Data from adults treated in 8 controlled randomised clinical studies have been reviewed, 780 patients received dexrazoxane plus chemotherapy and 789 received chemotherapy alone. The rate of death on study was higher with the combination dexrazoxane plus chemotherapy (5.0%) compared to chemotherapy alone (3.4%). The difference was not statistically significant and no consistent cause was apparent, however a contribution of dexrazoxane to the difference cannot be ruled out.

5.2 Pharmacokinetic properties

After intravenous administration to cancer patients, serum kinetics of dexrazoxane generally follow an open two-compartment model with first-order elimination. The maximum plasma concentration observed after a 12-15 minute infusion of 1000 mg/m^2 is around 80 µg/ml with area under the plasma concentration-time curve (AUC) of 130 ± 15 mg.h/l. The plasma concentrations declined thereafter with an average half-life value of 2.2 ± 1.2 hours. The apparent volume of distribution is 44.0 ± 3.9 l, suggesting that dexrazoxane distributes mainly in the total body water. The total body clearance of dexrazoxane in adults is estimated at 14.4 ± 1.6 l/h. {(Invented) Name} and its metabolites were detected in the plasma and urine of animals and man. The majority of the administered dose is eliminated in urine mainly as unchanged dexrazoxane. The total urinary excretion of unchanged dexrazoxane is in the order of 40%. Plasma protein binding of dexrazoxane is low (2%) and it does not penetrate into the cerebrospinal fluid to a clinically significant extent. Active substance clearance may be reduced in elderly patients and patients with low creatinine clearance. There is limited data on pharmacokinetic interactions with chemotherapeutic agents other than doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil and paclitaxel. No studies were conducted in the elderly and subjects with hepatic or renal impairment.

5.3 Preclinical safety data

Preclinical studies indicate that, with repeated dexrazoxane administration, the primary target organs are those of rapid cell division: bone marrow, lymphoid tissue, testes and gastrointestinal mucosa. The {(Invented) Name} dosing schedule is a primary factor in the degree of tissue toxicity produced. A single high dose is better tolerated than the same dose administered several times a day. Dexrazoxane has been shown to possess mutagenic activity. The carcinogenic potential of dexrazoxane has not been investigated. However prolonged administration of high doses of razoxane, the racemic mixture of which dexrazoxane is the S (+)-enantiomer, has been associated with the development of secondary malignancies (primarily acute myeloid leukaemia). Animal reproduction studies reveal that razoxane is embryotoxic to mice, rats and rabbits and also teratogenic to rats and mice, although a different dosing schedule was used compared to that used in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

{(Invented) Name} 500 mg powder for solution for infusion
Dexrazoxane

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What {(Invented) Name} is and what it is used for
2. Before you are given {(Invented) Name}
3. How {(Invented) Name} is used
4. Possible side effects
5. How to store {(Invented) Name}
6. Further information

1. WHAT {(Invented) Name} IS AND WHAT IT IS USED FOR

{(Invented) Name} contains a substance called dexrazoxane. This substance belongs to a group of medicines which protect the heart (cardioprotective medicines).

{(Invented) Name} is used to prevent heart damage when medicines called doxorubicin or epirubicin are used during breast cancer treatment in adults.

2. BEFORE YOU ARE GIVEN {(Invented) Name}

You must not be given {(Invented) Name}
- If you are under 18 years old.
- If you are allergic (hypersensitive) to dexrazoxane.
- If you are breast-feeding (see also "Pregnancy and breast-feeding").

If any of the above apply, you must not be given this medicine.

Before you are given {(Invented) Name}, tell your doctor
- If you have or have had liver or kidney problems.
- If you have or have had a heart attack, heart failure, uncontrolled chest pain and heart valve problems.
- If you are pregnant or plan to become pregnant (see also "Pregnancy and breast-feeding").
- If you are allergic to dexrazoxane or razoxane.

You should also be aware that:
- Your doctor may carry out tests before and during the treatment with {(Invented) Name} to see how well the treatment is working and to check the function of some of your organs, such as your heart, kidneys or liver.
- Your doctor may carry out blood tests during the treatment with {(Invented) Name} to monitor your bone marrow function. If you are receiving high-dose cancer treatment (e.g. chemotherapy or radiation) and are also being treated with high doses of {(Invented) Name}, your bone marrow function may be reduced. This may affect the production of red blood cells, white blood cells, and platelets.
- {(Invented) Name} may increase the risk of developing leukaemia (cancer of the blood).

- During treatment with {(Invented) Name}, women of childbearing potential and men should use effective contraception. Men should continue using contraception for at least three months after {(Invented) Name} treatment has been stopped (see also "Pregnancy and breast-feeding").
- The combination of {(Invented) Name} with your cancer treatment may increase the risk of blood clots.
- **If {(Invented) Name} powder or solution gets on your skin**, tell your doctor straight away. You or your doctor should immediately rinse the affected area thoroughly with water.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
- You will not be given {(Invented) Name} if you are pregnant or had planned to become pregnant, unless your doctor decides it is necessary.
- Women of childbearing potential should use effective contraception during treatment with {(Invented) Name}.
- Men should use effective contraception during treatment with {(Invented) Name} and for at least three months after {(Invented) Name} treatment has been stopped.
- Stop breast-feeding while you are receiving {(Invented) Name} treatment.

Ask your doctor or pharmacist for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
Tiredness has been reported with {(Invented) Name} treatment. Therefore if you feel sleepy, do not drive or use machines.

3. HOW {(Invented) Name} IS USED

How {(Invented) Name} is given to you
This medicine is prepared and given to you by your doctor or other medical staff. The dose you will receive is decided by your doctor.
- {(Invented) Name} is given as a drip (infusion) into a vein over about 15 minutes. This will start approximately 30 minutes before your cancer treatment (doxorubicin and/or epirubicin).

If you think you have been given more {(Invented) Name} than you should
If you are given too much {(Invented) Name}, tell your doctor or nurse straight away. You may experience some of the side effects listed in section 4, "Possible side effects".

4. POSSIBLE SIDE EFFECTS

Like all medicines, {(Invented) Name} can have side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention:
Very common (affecting more than 1 in 10 patients):
- Frequent infections, fever, sore throat, unexpected bruising and bleeding (signs of blood disorders such as low red blood cell counts, low white blood cell counts, low level of platelets and low level of granulocytes. Your blood counts may however return to normal after each treatment cycle)

Common (affecting less than 1 in 10 patients):
- Swelling and reddening of a vein

Uncommon (affecting less than 1 in 100 patients):
- Leukaemia (cancer of the blood)

– Sudden loss of consciousness
– Swelling and pain in one part of the body that can be caused by blood clotting within vein
– Tissue swelling in limbs

The following side effects have been reported in very few patients during treatment with {(Invented) Name}:
– Allergic reactions including itching, rash, facial/throat swelling, wheezing, breathlessness or difficult breathing, changes in levels of consciousness, hypotension
– Sudden onset of shortness of breath, coughing up blood and chest pain (signs of blood clot in the lung)

If you get any of the above, tell your doctor straight away or go to the nearest emergency unit.

Other side effects include:

Very common (affecting more than 1 in 10 patients):
– Hair loss
– Vomiting, mouth sores, nausea
– Weakness

Common (affecting less than 1 in 10 patients):
– Diarrhoea, stomach pain, constipation, fullness in stomach and loss of appetite
– Decreased heart muscle function, fast heart beat
– Pain, redness and swelling of the moist lining of the internal passageways such as the airways or food pipe
– Nail disorders such as blackening
– Skin reaction such as swelling, redness, pain, burning sensation, itching at the site of injection
– Tingling or numbness of the hands or feet, dizziness, headache
– Discharge from the eye with itching, redness and swelling
– Tiredness, generally feeling unwell
– Slight fever
– Abnormal liver function test results

Uncommon (affecting less than 1 in 100 patients)
– Increase in blood cell counts
– Vertigo, ear infection
– Bleeding, tender or enlarged gums, oral thrush
– Thirst

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE {(Invented) Name}

[To be completed nationally]

6. FURTHER INFORMATION

What {(Invented) Name} contains

[To be completed nationally]

What {(Invented) Name} looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

INFORMATION FOR HEALTHCARE PROFESSIONALS

{(Invented) Name} 500 mg powder for solution for infusion
Dexrazoxane

[To be completed nationally]